PATENT-TERM



# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|---|---|---|
| In re | : | U.S. Patent No. 4,997,841 |
| Issued | : | March 5, 1991 |
| Inventors | : | Alexander W. Oxford, Darko Butina and Martin R. Owen |
| Assignee | : | Glaxo Group Limited |
| For | : | INDOLE DERIVATIVES |



Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231



Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM under 35 U.S.C. §156 with regard to U.S. Patent No. 4,997,841.

The Commissioner is hereby authorized to charge Deposit Account No. 07-1392 in the amount of $1,060.00 to cover the application fee. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit overpayment to Account No. 07-1392 . Duplicate copies of this letter are enclosed.

**CERTIFICATION UNDER 37 C.F.R. § 1.10**

I hereby certify that this Application for Extension of Patent Term and the documents referred to therein are being deposited with the United States Postal Service on this date March 30, 1998 in an envelope as "Express Mail Post Office to Addressee," Mailing Label Number EM 484 295 648 US addressed to the: Commissioner of Patents and Trademarks, Box Patent Ext., Washington, D.C. 20231.

04/08/1998 ACURAM 00000014 071392 4997841
01 FC:111 1120.00 CH

Shah R. Makujina
(Type or print name of person mailing paper)

(Signature of person mailing paper)

Please address all communications relating to the enclosed APPLICATION FOR EXTENSION OF PATENT TERM to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
Telephone No. (919) 483-2723

Respectfully submitted,
By: Glaxo Wellcome Inc.

March 30, 1998
Date

Shah R. Makujina
Reg. No. 41,174
Attorney for Applicant

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
Phone: (919) 483-1276
Facsimile: (919) 483-7988

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In Re | : | U.S. Patent No. 4,997,841 |
| Issued | : | March 5, 1991 |
| Inventors | : | Alexander W. Oxford, Darko Butina and Martin R. Owen |
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Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

## APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

Sir:

Applicant, Glaxo Wellcome Inc., a corporation of the State of North Carolina (formerly Glaxo Inc.) represents that it is a subsidiary of Glaxo Group Limited, a company incorporated in England, and agent thereof for purposes of filing this Application for Extension of Patent Term for U.S. Patent 4,997,841 pursuant to a grant of Power of Attorney. See EXHIBIT 1. Applicant further represents pursuant to 35 U.S.C. § 156(d)(1), that Glaxo Group Limited is the record owner and assignee of the entire interest in and to Letters Patent of the United States of America No. 4,997,841 granted to Alexander W. Oxford, Darko Butina and Martin R. Owen for INDOLE DERIVATIVES recorded in the United States Patent and Trademark Office on August 25, 1988 Reel 4938, Frames 647-648. A copy of said assignment is attached as EXHIBIT 2.

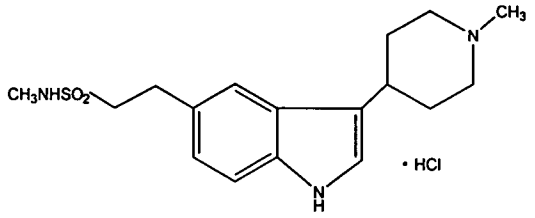
Applicant further represents, pursuant to 37 C.F.R. § 1.785(d), that it is the holder of the regulatory approval granted by the Food and Drug Administration ("FDA") for AMERGE™(naratriptan hydrochloride) Tablets (hereinafter, "AMERGE™ Tablets"). See EXHIBIT 3.

Applicant hereby presents this application for extension of patent term under 35 U.S.C §156 according to the format set forth in 37 C.F.R. § 1.740(a).

(1) This application for extension is based upon the regulatory review period before the FDA of Applicant's Approved Product, AMERGE™ Tablets. The only active ingredient in AMERGE™ Tablets is naratriptan hydrochloride. A copy of the package insert approved by the FDA as part of New Drug Application ("NDA") 20-763 for the Approved Product is attached hereto as EXHIBIT 4. Identification of the Approved Product, AMERGE™ Tablets, is provided as follows:

Chemical Name: N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride

Structural Formula:




Molecular Formula: $C_{17}H_{25}N_3O_2S \cdot HCl$

Molecular Weight: 371.93 daltons

(2) The Approved Product, AMERGE™ Tablets, was subject to regulatory review under Federal Food, Drug and Cosmetic Act, section 505 (21 U.S.C. § 355).

(3) Applicant seeks an extension of patent term for the human drug product, AMERGE™ Tablets. On February 10, 1998, Applicant received permission from the FDA under section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for the commercial marketing or use of naratriptan hydrochloride.

(4) Naratriptan hydrochloride is the active ingredient in AMERGE™ Tablets. Naratriptan hydrochloride has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60 day period, which will expire on April 10, 1998.

(6) The complete identification of the patent for which extension of term is being sought is as follows:

| | | |
|---|---|---|
| In Re | : | U.S. Patent No. 4,997,841 |
| Issued | : | March 5, 1991 |
| Inventors | : | Alexander W. Oxford, Darko Butina and Martin R. Owen |
| Assignee | : | Glaxo Group Limited |
| For | : | INDOLE DERIVATIVES |

(7) A complete copy of the patent identified in paragraph (6) above is appended hereto as EXHIBIT 5.

(8) Copies of the receipts of all maintenance fee payments made with respect to U.S. Patent 4,997,841 are attached hereto as EXHIBIT 10.

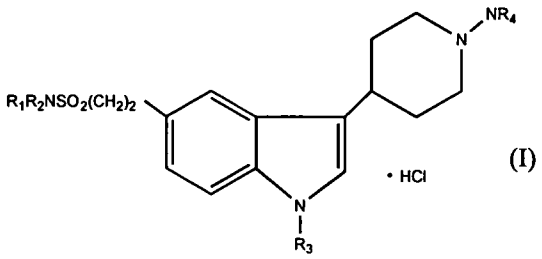
(a) No certificate of correction or reexamination certificate exists in respect of U.S. Patent 4,997,841.

(b) A terminal disclaimer in respect of U.S. Patent No. 4,997,841 is included as EXHIBIT 6. The terminal part of U.S. Patent 4,997,841 was disclaimed against the full statutory term of any patent issuing from Application No. 07/231,260. Application No. 07/570,513 was filed on October 9, 1990 as a continuation of Application No. 07/231,260 which was abandoned. Application No. 07/570,513 issued into U.S. Patent 5,066,660 on November 19, 1991 having an expiration date of November 19, 2008 which is later than that of the August 12, 2008 expiration of U.S. Patent No. 4,997,841 for which Applicants are seeking extension. U.S. Patent 5,066,660 was abandoned in March of 1995 by withholding the May 19, 1995 maintenance fee payment. Thus the term of U.S. Patent No. 4,997,841 for which Applicants are seeking extension should not be shortened by the disclaimer.

(9) United States Patent Number 4,997,841 claims the active ingredient in the Approved Product AMERGE™ Tablets, pharmaceutical compositions comprising the active ingredient in the Approved Product and methods of treating migraine with the active ingredient in the Approved Product. Applicant hereinbelow lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the Approved Product, pharmaceutical compositions comprising the Approved Product and methods of using the Approved Product.

(a) Claim 1 reads as follows:

A compound of formula (I)




(I)

wherein

$R_1$ represents a hydrogen atom or a $C_{1-6}$ alkyl group;

$R_2$ represents a hydrogen atom or a $C_{1-6}$ alkyl group;

$R_3$ represents a hydrogen atom;

$R_4$ represents a hydrogen atom or a $C_{1-3}$ alkyl group;

or a pharmaceutically acceptable salt s [*sic*] solvate thereof.

---

Claim 1 reads on the Approved Product since in the active ingredient of the Approved Product, N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5- ethanesulfonamide monohydrochloride,

$R_1$ is hydrogen;

$R_2$ is $CH_2$ which is a $C_1$ alkyl group;

$R_3$ is hydrogen; and

$R_4$ is $CH_3$ which is a $C_1$ alkyl group.

(b) Claim 2 reads as follows:

A compound according to claim 1 wherein in the formula (I) $R_1$ represents a hydrogen atom or $C_{1-3}$ alkyl group.

---

Claim 2 reads on the Approved Product since in the active ingredient of the Approved Product, N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5- ethanesulfonamide monohydrochloride,

$R_1$ is hydrogen.

(c) Claim 3 reads as follows:

A compound according to claim 1 wherein in the formula (I) $R_2$ represents a hydrogen atom or $C_{1-3}$ alkyl group.

---

Claim 3 reads on the Approved Product since in the active ingredient of the Approved Product, N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5- ethanesulfonamide monohydrochloride,

$R_2$ is $CH_2$ which is $C_1$ alkyl.

(d) Claim 4 reads as follows:

A compound according to claim 1 wherein in the formula (I) $R_2$ represents a $C_{1-3}$ alkyl group.

---

Claim 4 reads on the Approved Product since in the active ingredient of the Approved Product, N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5- ethanesulfonamide monohydrochloride,

$R_2$ is $CH_2$ which is $C_1$ alkyl.

(e) Claim 5 reads as follows:

A compound according to claim 1 wherein in the formula (I) $R_4$ represents a $C_{1-3}$ alkyl group.

---

Claim 5 reads on the Approved Product since in the active ingredient of the Approved Product, N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5- ethanesulfonamide monohydrochloride,

$R_4$ is $CH_3$ which is $C_1$ alkyl.

(f) Claim 6 reads as follows:

A compound according to claim 1 which is N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide or a pharmaceutically acceptable salt or solvate thereof.

---

Claim 6 reads on the Approved Product since the active ingredient of the Approved Product is

N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride which is a pharmaceutically acceptable salt of N-Methyl-3-(1-methyl-4-piperidinyl)- 1H-indole-5-ethanesulphonamide.

(g) Claim 11 reads as follows:

A pharmaceutical composition for use in the treatment of conditions associated with cephalic pain which comprises an effective amount to treat conditions associated with cephalic pain of at least one compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers or excipients.

---

Claim 11 reads on the Approved Product since

the active ingredient of the Approved Product, N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride is a pharmaceutically acceptable salt of a compound of formula (I);

is indicated for the treatment of migraine which is defined in the patent specification as one of several types of cephalic pain (column 2; lines 30-35);

is administered in single doses of 1 and 2.5 mg of AMERGE Tablets which is an effective amount to treat acute migraines in adults; and

is formulated with croscarmellose sodium, hydroxypropylmethylcellulose, lactose, magnesium stearate, microcrystalline cellulose, triacetin, titanium dioxide, iron oxide yellow, and indigo carmine aluminum lake (FD&C Blue No. 2) which include pharmaceutically acceptable carriers or excipients.

(h) Claim 12 reads as follows:

A pharmaceutical composition as claimed in claim 11 wherein the conditions associated with cephalic pain are migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with vascular disorders.

---

Claim 12 reads on the Approved Product since the Approved Product is indicated for the treatment of migraine.

(i) Claim 13 reads as follows:

A pharmaceutical composition according to claim 11 adapted for oral, parenteral or intranasal administration.

---

Claim 13 reads on the Approved Product since

the active ingredient of the Approved Product, N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride is a pharmaceutically acceptable salt of a compound of formula (I);

is indicated for the treatment of migraine which is defined in the patent specification as one of several types of cephalic pain (column 2; lines 30-35);

is administered in single doses of 1 and 2.5 mg of AMERGE Tablets which is an effective amount to treat acute migraines in adults;

is formulated with croscarmellose sodium, hydroxypropylmethylcellulose, lactose, magnesium stearate, microcrystalline cellulose, triacetin, titanium dioxide, iron oxide yellow, and indigo carmine aluminum lake (FD&C Blue No. 2) which include pharmaceutically acceptable carriers or excipients; and

is formulated as a tablet for oral administration.

(j) Claim 14 reads as follows:

A pharmaceutical composition according to claim 11 which is formulated in unit dosage form comprising 0.1 mg to 100 mg of active ingredient.

---

Claim 14 reads on the Approved Product since the Approved Product is formulated in unit dosages of 1 mg and 2.5 mg of the active ingredient and is indicated for the treatment of migraine.

(k) Claim 15 reads as follows:

A pharmaceutical composition according to claim 13 which is formulated in unit dosage form comprising 0.1 mg to 100 mg of active ingredient.

---

Claim 15 reads on the Approved Product since the Approved Product is formulated as a tablet for oral administration in unit dosages of 1 mg and 2.5 mg of the active ingredient.

(l) Claim 16 reads as follows:

A method of treating a human susceptible to or suffering from migraine cluster headache, chronic paroxysmal hemicrania or headache associated with vascular disorders which comprises administering an effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or solvate thereof.

---

Claim 16 reads on the Approved Product since the Approved Product is a pharmaceutically acceptable salt of a compound of formula (I) and is indicated for the treatment of migraine in humans.

(m) Claim 17 reads as follows:

A method of treating a human susceptible to or suffering from migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with vascular disorders which comprises administering pharmaceutical composition according to claim 11.

---

Claim 17 reads on the Approved Product since the Approved Product is

a pharmaceutically acceptable salt of a compound of formula (I);

is formulated with croscarmellose sodium, hydroxypropylmethylcellulose, lactose, magnesium stearate, microcrystalline cellulose, triacetin, titanium dioxide, iron oxide yellow, and indigo carmine aluminum lake (FD&C Blue No. 2) which include pharmaceutically acceptable carriers or excipients; and

is indicated for the treatment of migraine.

(n) Claim 18 reads as follows:

A method of treating a human susceptible to or suffering from migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with vascular disorders which comprises administering a pharmaceutical composition according to claim 13.

---

Claim 18 reads on the Approved Product since

the active ingredient of the Approved Product, N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride is a pharmaceutically acceptable salt of a compound of formula (I);

is indicated for the treatment of migraine which is defined in the patent specification as one of several types of cephalic pain (column 2; lines 30-35);

is administered in single doses of 1 and 2.5 mg of AMERGE Tablets which is an effective amount to treat acute migraines in adults;

is formulated with croscarmellose sodium, hydroxypropylmethylcellulose, lactose, magnesium stearate, microcrystalline cellulose, triacetin, titanium dioxide, iron oxide yellow, and indigo carmine aluminum lake (FD&C Blue No. 2) which include pharmaceutically acceptable carriers or excipients; and

is formulated as a tablet for oral administration.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) necessary to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) Effective Date of IND
The effective date of IND 48,120 is July 5, 1995, thirty days after its initial submission. See EXHIBIT 8.

(b) Issue Date of Patent
U.S. Patent No. 4,997,841 issued March 5, 1991 and claims a new drug. See EXHIBIT 5.

(c) Submission Date of NDA
The NDA for AMERGE™ Tablets was submitted on December 4, 1996. The NDA was designated as NDA 20-763. See EXHIBIT 9.

(d) Approval Date of NDA
NDA 20-763 for AMERGE™ Tablets was approved by the FDA on February 10, 1998. See EXHIBIT 3.

(11) A brief description of each significant activity undertaken by Applicant during the IND and NDA regulatory periods is presented in chronological form and is attached hereto as EXHIBITS 8 and 9, "Document Chronologies / Due Diligence Log".

(a) The Due Diligence Log reflects significant communications between Applicant and FDA during regulatory periods. Such communications include, but are not limited to: submission of pre-clinical reports; registration of clinical protocols and amendments thereof; registration of clinical investigators and amendments thereof; submission of adverse event reports; submission of IND Annual Reports, etc.

(b) Periods between such communications enumerated in the Due Diligence Log may reflect Applicant's diligent undertaking of the necessary clinical studies and other activities required by the FDA in order to obtain approval for Applicant's product.

(12) Applicant is of the opinion that U.S. Patent 4,997,841 is eligible for a 693-day extension.

(a) Applicant has satisfied the eligibility criteria necessary to obtain a patent term extension pursuant to 35 U.S.C. § 156.

(1) 35 U.S.C. § 156(a)
U.S. Patent 4,997,841 claims a drug product, pharmaceutical compositions and methods of using a drug product.

(2) 35 U.S.C. § 156(a)(1)
The term of U.S. Patent 4,997,841 has not expired before submission of this application.

(3) 35 U.S.C. § 156(a)(2)
The term of U.S. Patent 4,997,841 has never been extended.

(4) 35 U.S.C. § 156(a)(3)
The application for extension is submitted by the owner of record in accordance with the requirements of 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 *et seq.*

(5) 35 U.S.C. § 156(a)(4)
The Approved Product, AMERGE™ Tablets, has been subject to a regulatory review period before its commercial marketing or use.

(6) 35 U.S.C. § 156(a)(5)(A)
The commercial marketing or use of the Approved Product, AMERGE™ Tablets, after the regulatory review period is the first permitted commercial marketing or use of the Approved Product under the provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) under which such regulatory review period occurred.

(b) Applicant herewith, claims a patent term extension of 693 days for U.S. Patent 4,997,841 pursuant to 35 U.S.C. § 156(g):

(1) One-half of the IND regulatory review period for the Approved Product beginning March 5, 1991 (the IND period occurring after the date of the issuance of U.S. Patent 4,997,841) and ending on December 3, 1996 (one day prior to the date on which the NDA for the Approved Product was initially submitted) such period being equal to 259 days. See EXHIBIT 7.

(2) The full term of the NDA regulatory review period commencing December 4, 1996 (the date NDA 20-763 for the Approved Product was submitted) and ending on February 10, 1998 (the date on which NDA 20-763 was approved), such period being equal to 434 days. See EXHIBIT 7.

(3) The sum of one-half the IND period and the NDA period equals 693 days.

(c) Applicant herewith, claims an expiration date of July 5, 2010 for U.S. Patent 4,997,841 pursuant to 35 U.S.C. § 156(c).

(1) The expiration of U.S. Patent 4,997,841 20 years from its first U.S. filing date is August 12, 2008 pursuant to the Uruguay Round Agreements Act, Public Law 103-465 (1994).

(2) Extending the August 12, 2008 expiration by 693 days would result in an expiration date of July 5, 2010.

(3) The extended term expires before the 14 year cap under 35 U.S.C. § 156(c)(3) which occurs on February 10, 2012. See EXHIBIT 7.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension.

(14) The Commissioner of Patents and Trademarks is authorized to charge deposit account 07-1392 in the amount of $1,060.00 for receiving and acting upon this application for extension of term. In the event the actual fee differs from that specified above, it is requested that the overpayment be charged or the underpayment credited.

(15) Inquiries and correspondence relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.

Patent Counsel

Glaxo Wellcome Inc.

Five Moore Drive

Research Triangle Park, NC 27709

(919) 483-2723

(16) A duplicate of the application papers, certified as such is attached hereto.

(17) Submitted herewith is a Declaration by Shah R. Makujina, Patent Attorney for Glaxo Wellcome Inc., which meets the criteria set forth in 37 C.F.R. § 1.740(b).

The undersigned hereby certifies that this Application for Extension of Patent Term under 35 U.S.C. § 156 and the declaration as set forth in 37 C.F.R. § 1.740(b) are being submitted as duplicate originals and three copies, a Certificate of Express Mail under 37 C.F.R. §1.10 as an original and four copies, and accompanying EXHIBITS as five copies.

Respectfully submitted,

By: Glaxo Wellcome Inc.

March 30, 1998
Date

Shah R. Makujina
Reg. No. 41,174
Attorney for Applicant

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
Phone: (9i9) 483-1276
Facsimile: (919) 483-7988

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In Re | : | U.S. Patent No. 4,997,841 |
| Issued | : | March 5, 1991 |
| Inventors | : | Alexander W. Oxford, Darko Butina and Martin R. Owen |
| Assignee | : | Glaxo Group Limited |
| For | : | INDOLE DERIVATIVES |



Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

## Declaration Under 37 C.F.R. § 1.740(b)

To the Commissioner of Patents and Trademarks:

I, Shah R. Makujina, residing in Durham, North Carolina, declare as follows:

(1) That I am a patent attorney authorized to practice before the United States Patent and Trademark Office and that my registration number is 41,174.

(2) That I make this declaration as a Patent Attorney for Glaxo Wellcome Inc., a corporation of the State of North Carolina having a place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709 and have general authority to act on its behalf in patent matters.

(3) That Glaxo Group Limited is the assignee of the entire right, title and interest in United States Patent 4,997,841 issued March 5, 1991 (hereinafter "Patent") and has authorized Glaxo Wellcome Inc. pursuant to the attached Power of Attorney to file the instant Application for Extension of Patent Term. See Exhibit 1.

(4) That I have general authority in patent matters to act on behalf of Glaxo Group Limited pursuant to the attached Power of Attorney.

(5) That I have reviewed and understand the contents of the Application for Extension of Patent Term submitted herewith on behalf of Glaxo Wellcome Inc. requesting a 693-day extension of the term of the Patent is justified under 35 U.S.C. § 156 and applicable regulations.

(6) That I believe that the Patent is subject to extension pursuant to 37 C.F.R. § 1.710.

(7) That I believe that a 693-day extension of the term of the Patent is justified under 35 U.S.C. §156 and applicable regulations.

(8) That I believe the Patent meets the conditions for the extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 4,997,841 and any extensions thereof.

Respectfully submitted,

March 30, 1998
Date

Shah R. Makujina
Reg. No. 41,174
Attorney for Applicant

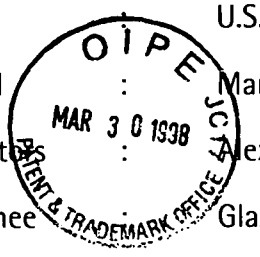
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
Phone: (919) 483-1276
Facsimile: (919) 483-7988

# EXHIBIT 1

Declaration and Power of Attorney
37 C.F.R. 3.73(b)

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re : U.S. Patent No. 4,997,841




Issued : March 5, 1991

Inventors : Alexander W. Oxford, Darko Butina and Martin R. Owen

Assignee : Glaxo Group Limited

For : INDOLE DERIVATIVES

Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

**Declaration and Power of Attorney**

**37 C.F.R. § 3.73(b)**

To the Commissioner of Patents and Trademarks:

I, Graham George Brereton, declare as follows:

That I am an Attorney of Glaxo Group Limited, a company incorporated in England and having its registered address at Glaxo Wellcome House, Berkeley Avenue, Greenford, United Kingdom, UB6 ONN, by virtue of a Power of Attorney granted by Glaxo Group Limited which empowers me to act on behalf of Glaxo Group Limited.

That pursuant to 37 C.F.R. § 3.73(b) and 35 U.S.C. § 156(d)(1) , Glaxo Group Limited is the record owner and assignee of the entire interest in and to U.S. Patent No. 4,997,841 recorded in the United States Patent and Trademark Office on August 25, 1988. Reel 4938, Frames 647-648.

That I have reviewed the evidentiary documents for the aforesaid chain of title and hereby certify pursuant to 37 C.F.R. § 3.73(b) that, to the best of my knowledge and belief, title is in the assignee, Glaxo Group Limited by virtue of the above noted assignment.

That Glaxo Group Limited does hereby make, constitute and appoint Glaxo Wellcome Inc. organized under the laws of North Carolina, having their principal place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709, United States of America as its special, true and lawful agent and attorney for the limited purpose of preparing and filing with the U.S. Patent and Trademark office an Application for Extension of Patent Term pursuant to 35 U.S.C. § 156 in respect of U.S. Patent No. 4,997,841 which Patent is owned by Glaxo Group Limited, and prosecuting said Application; and to do and perform each and every act in connection with the above stated purpose which Glaxo Wellcome Inc. deems necessary or

desirable.

That Glaxo Group Limited herein issues general authority to the following attorney(s) and/or agent(s), each of Glaxo Wellcome Inc., to prosecute this Application and transact all business in the Patent and Trademark Office connected therewith.

| | | | |
|---|---|---|---|
| David J. Levy | Reg. No. 27,655 | James P. Riek | Reg. No. 39,009 |
| Shah R. Makujina | Reg. No. 41,174 | Charles E. Dadswell | Reg. No. 35,851 |
| Robert T. Hrubiec | Reg. No. 36,392 | Robert H. Brink | Reg. No. 36,094 |
| Frank P. Grassler | Reg. No. 31,164 | Karen L. Prus | Reg. No. 39,337 |

That any inquiries and correspondence relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-2723

The undersigned further declares that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 4,997,841 and any extensions thereof.

Glaxo Group Limited,

March 25, 1998

Date

Graham George Brereton
Attorney for Glaxo Group Limited

# EXHIBIT 2

Assignment of
Application for Letters Patent of the United States

UNITED STATES DEPARTMENT OF COMMERCE
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| ASSIGNOR: 001 OXFORD, ALEXANDER W. | DOC DATE: 08/05/88 |
| ASSIGNOR: 002 BUTINA, DARKO | DOC DATE: 08/05/88 |
| ASSIGNOR: 003 OWEN, MARTIN R. | DOC DATE: 08/05/88 |

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DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 GLAXO GROUP LIMITED, CLARGES HOUSE, 6/12 CLARGES STREET, LONDON W1Y 8DH, ENGLAND

| | | | |
|---|---|---|---|
| SERIAL NUMBER | 7-231274 | FILING DATE | 08/12/88 |
| PATENT NUMBER | | ISSUE DATE | 00/00/00 |

TITLE OF INVENTION: INDOLE DERIVATIVES

INVENTOR: 001 OXFORD, ALEXANDER W.
INVENTOR: 002 BUTINA, DARKO
INVENTOR: 003 OWEN, MARTIN R.

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Groups 3/4

I, RICHARD GRAHAM ROSSER, of the City of London, Notary Public duly admitted and sworn practising in the said City,

DO HEREBY CERTIFY AND ATTEST:

THAT the signatures "Alexander William Oxford" "Darko Butina" and "Martin Richard Owen" set and subscribed at foot of the hereunto annexed Assignment are in each case genuine, the same having been duly subscribed thereto by ALEXANDER WILLIAM OXFORD, DARKO BUTINA, and MARTIN RICHARD OWEN, whose identities I attest.

IN TESTIMONY WHEREOF I have hereunto set my hand and affixed my Seal of Office in the City of London aforesaid, this tenth day of August One thousand nine hundred and eighty-eight.

# ASSIGNMENT

WHEREAS, I (we), ALEXANDER WILLIAM OXFORD, DARKO BUTINA and MARTIN RICHARD OWEN whose post office address(es) appear(s) below, hereinafter referred to as ASSIGNOR, have invented certain new and useful improvements in INDOLE DERIVATIVES

☒ for which an application for United States Letters Patent was filed on _____, Serial No. _____; and,

☒ for which an application for United States Letters Patent was executed on 5th August 1988; and,

☐ for which International Application No. _____ designating the United States of America was filed on _____; and,

WHEREAS, GLAXO GROUP LIMITED, whose post office address is Clarges House, 6/12 Clarges Street, London W1Y 8DH, England

hereinafter referred to as ASSIGNEE, is desirous of acquiring the entire right, title and interest in and to the same in the United States;

NOW, THEREFORE, for good and valuable consideration, receipt of which is hereby acknowledged, I (we), ASSIGNOR, by these presents do sell, assign and transfer unto said ASSIGNEE, the entire right, title, and interest in and to said invention and application throughout the United States of America and in and to any and all Letters Patent which may be granted therefor in the United States of America, including any and all Letters Patent granted on any division, continuation, continuation-in-part and reissue of said application.

ALSO, ASSIGNOR hereby agrees to execute any documents that legally may be required in connection with the filing, prosecution and maintenance of said application or any other patent application(s) in the United States for said invention, including additional documents that may be required to affirm the rights of ASSIGNEE in and to said invention, all without further consideration. ASSIGNOR also agrees without further consideration and at ASSIGNEE'S expense, to identify and communicate to ASSIGNEE at ASSIGNEE'S request documents and information concerning the invention that are within ASSIGNOR'S possession or control, and to provide further assurances and testimony on behalf of ASSIGNEE that lawfully may be required of ASSIGNOR in respect of the prosecution, maintenance and defense of any patent application or patent encompassed within the terms of this instrument. ASSIGNOR'S obligations under this instrument shall extend to ASSIGNOR'S heirs, executors, administrators and other legal representatives.



ASSIGNOR hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all Letters Patent referred to above to ASSIGNEE, as the ASSIGNEE of the entire right, title and interest in and to the same, for ASSIGNEE'S sole use and behoof; and for the use and behoof of ASSIGNEE'S legal representatives and successors, to the full end of the term for which such Letters Patent may be granted, as fully and entirely as the same would have been held by ASSIGNOR had this assignment and sale not been made.

ALEXANDER WILLIAM OXFORD
Assignor Name

60 Green Drift, Royston,
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City

England
State (Zip) or Country

5th August 1988
Date

Ware, Hertfordshire, England
Where Signed

Alexander William Oxford
Signature

_____ ss.
_____

Before me personally appeared said _____ and acknowledged this
(Assignor Name)
instrument to be his (her) free act and deed _____ day of _____, 19___.

JOINT ASSIGNMENT
(WITNESS)

DARKO BUTINA
Assignor Name

81 High Street, Arlesey,
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Darko Butina
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Witness: (not required)

Print/Type Name

Signature

Witness: (not required)

Print/Type Name

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MARTIN RICHARD OWEN
Assignor Name

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5th August 1988
Date

WARE, HERTFORDSHIRE, ENGLAND
Where Signed

Martin Richard Owen
Signature

Witness: (not required)

Print/Type Name

Signature

Witness: (not required)

Print/Type Name

Signature

REEL 4938 FRAME 648

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Assignor Name

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City

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Witness: (not required)

Print/Type Name

Signature

Date

Where Signed

Signature

Witness: (not required)

Print/Type Name

Signature

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AUG 25 88

(See following Page(s) for Plural Assignors)


# EXHIBIT 3

FDA Approval Letter for

AMERGE™(naratriptan hydrochloride) Tablets

NDA 20-763

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-763

FEB 10 1998

Glaxo Wellcome Inc.
Attention: James E. Murray
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Mr. Murray:

Please refer to your new drug application dated December 4, 1996, received December 4, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amerge (naratriptan) 1 mg and 2.5 mg tablets.

We acknowledge receipt of the following submissions:

| | | | |
|---|---|---|---|
| December 16, 1996 | April 15, 1997 | July 3, 1997 | September 11, 1997 |
| January 14, 1997 | May 1, 1997 (2) | July 9, 1997 (2) | October 7, 1997 |
| January 23, 1997 | May 8, 1997 | July 25, 1997 | October 17, 1997 |
| February 7, 1997 | May 15, 1997 | July 29, 1997 | November 21, 1997 |
| February 12, 1997 | May 27, 1997 (2) | August 1, 1997 | November 26, 1997 |
| February 19, 1997 | June 3, 1997 | August 5, 1997 | December 1, 1997 (2) |
| February 26, 1997 | June 6, 1997 | August 6, 1997 | December 15, 1997 |
| February 27, 1997 | June 10, 1997 | August 7, 1997 | December 17, 1997 |
| March 10, 1997 | June 24, 1997 | August 20, 1997 | January 15, 1998 |
| March 17, 1997 | June 26, 1997 | August 29, 1997 | January 16, 1998 |
| April 2, 1997 | June 30, 1997 | September 2, 1997 | |
| April 10, 1997 | July 1, 1997 | September 4, 1997 | |

The original User Fee goal date for this application was December 4, 1997. Your submission of November 21, 1997 extended the User Fee goal date to March 4, 1998.

This new drug application provides for the acute treatment of migraine headache.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

Please adopt the following dissolution method and specifications:

| | |
|---|---|
| Dosage Form: | Tablet |
| Strengths: | 1mg and 2.5 mg (n =6) |
| Apparatus: | USP Apparatus 1 (basket) |
| Medium: | 500 mL 0.1 M HCl at 37°C |
| Speed: | 100 rpm. |
| Sampling Times: | 15 minutes |
| Requirement: | Q= 80% in 15 minutes |

The approved expiration date is 24 months at controlled room temperature (per USP).

The final printed labeling (FPL) must be identical to the enclosed labeling text. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-763. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

**AMERGE™**
**(naratriptan hydrochloride)**
**Tablets**

**DESCRIPTION:** AMERGE Tablets contain naratriptan as the hydrochloride, which is a selective 5-hydroxytryptamine 1 receptor subtype agonist. Naratriptan hydrochloride is chemically designated as N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride, and it has the following structure:

**[Note to firm: place structure here]**

The empirical formula is C17H25N3O2S•HCl, representing a molecular weight of 371.93. Naratriptan hydrochloride is a white to pale yellow powder that is readily soluble in water. Each AMERGE Tablet for oral administration contains 1.11 or 2.78 mg of naratriptan hydrochloride equivalent to 1 or 2.5 mg of naratriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium; hydroxypropyl methylcellulose; lactose; magnesium stearate; microcrystalline cellulose; triacetin; and titanium dioxide, iron oxide yellow, and indigo carmine aluminum lake (FD&C Blue No.2) for coloring.

**CLINICAL PHARMACOLOGY:**
**Mechanism of Action:** Naratriptan binds with high affinity to 5-$HT_{1D}$ and 5-$HT_{1B}$ receptors and has no significant affinity or pharmacological activity at $5HT_{2-4}$ receptor subtypes or at adrenergic α1, α2, or ß; dopaminergic D1 or D2; muscarinic; or benzodiazepine receptors.

The therapeutic activity of naratriptan in migraine is generally attributed to its agonist activity at $5HT_{1D/1B}$ receptors. Two current theories have been proposed to explain the efficacy of $5HT_{1D/1B}$ receptor agonists in migraine. One theory suggests that activation of $5HT_{1D/1B}$ receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-$HT_{1D/1B}$ receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.

In the anesthetized dog, naratriptan has been shown to reduce carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. While the effect on blood flow was selective for the carotid arterial bed, increases in vascular resistance of up to 30% were seen in the coronary arterial bed. Naratriptan has also been shown to inhibit trigeminal nerve activity in rat and cat. In 10 human subjects with suspected coronary artery disease undergoing coronary artery catheterization, there was a 1% to 10% reduction in coronary artery diameter following subcutaneous injection of 1.5 mg of naratriptan.

**Pharmacokinetics:** Naratriptan tablets are well absorbed, with about 70% oral bioavailability. Following administration of a 2.5 mg tablet orally the peak concentrations are obtained in 2 to 3 hours. After administration of 1.0 mg or 2.5 mg tablets, the C max is somewhat (about 50%) higher in women (not corrected for mg/kg dose) than in men. During a migraine attack, absorption was slower, with a T max of 3 to 4 hours. Food does not affect the pharmacokinetics of naratriptan. Naratriptan displays linear kinetics over the therapeutic dose range.

The steady-state volume of distribution of naratriptan is 170 L. Plasma protein binding is 28 to 31% over the concentration range of 50 to 1000 ng/mL.

Naratriptan is predominantly eliminated in urine, with 50% of the dose recovered unchanged and 30% as metabolites in urine. In vitro, naratriptan is metabolized by a wide range of cytochrome P450 isozymes into a number of inactive metabolites.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

The mean elimination half life of naratriptan is 6 hours. The systemic clearance of naratriptan is 6.6 mL/min/kg. The renal clearance (220 mL/min) exceeds glomerular filtration rate, indicating active tubular secretion. Repeat administration of naratriptan tablets does not result in drug accumulation.

**Special Populations:**

**Age:** A small decrease in clearance (approximately 26%) was observed in healthy elderly subjects (65 to 77 years) compared to younger patients, resulting in slightly higher exposure (see PRECAUTIONS).

**Race:** The effect of race on the pharmacokinetics of naratriptan has not been examined.

**Renal Impairment:** Clearance of naratriptan was reduced by 50% in patients with moderate renal impairment (creatinine clearance 18 to 39 mL/min) compared to the normal group. Decrease in clearances resulted in an increase of mean half-life from 6 hours (healthy) to 11 hours (range: 7 to 20 hours). The mean C max increased by approximately 40%. The effects of severe renal impairment (creatinine clearance ≤ 15 mL/min) on the pharmacokinetics of naratriptan have not been assessed. (See CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

**Hepatic Impairment:** Clearance of naratriptan was decreased by 30% in patients with moderate hepatic impairment (Child-Pugh grade A or B). This resulted in an approximately 40% increase in the half-life (range: 8 to 16 hours). The effects of severe hepatic impairment (Child-Pugh grade C) on the pharmacokinetics of naratriptan have not been assessed. (See CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

**Drug Interactions:** In normal volunteers, coadministration of single doses of naratriptan tablets and alcohol did not result in substantial modification of naratriptan pharmacokinetic parameters.

From population pharmacokinetic analyses, coadministration of naratriptan and fluoxetine, beta-blockers, or tricyclic antidepressants did not affect the clearance of naratriptan.

Naratriptan does not inhibit monoamine oxidase (MAO) enzymes and is a poor inhibitor of P450; metabolic interactions between naratriptan and drugs metabolized by P450 or MAO are therefore unlikely.

Oral contraceptives: Oral contraceptives reduced clearance by 32% and volume of distribution by 22%, resulting in slightly higher concentrations of naratriptan. Hormone replacement therapy had no effect on pharmacokinetics in older female patients.

Smoking increased the clearance of naratriptan by 30%.

**CLINICAL TRIALS:** The efficacy of AMERGE Tablets in the acute treatment of migraine headaches was evaluated in six randomized, double blind, placebo controlled studies of which 4 used the recommended dosing regimen and were conducted as outpatient trials. Three of these studies enrolled adult patients who were predominately female (86%) and Caucasian (96%) with a mean age of 41 (range 18 to 65). One study enrolled adolescents with a mean age of 14 (range 12 to 17). In the adolescent study, 54% of the patients were female and 89% were Caucasian. In all studies, patients were instructed to treat at least one moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 4 hours after dosing. Associated symptoms such as nausea, vomiting, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of AMERGE Tablets or other medication was allowed 4 to 24 hours after the initial treatment for

recurrent headache. The frequency and time to use of these additional treatments were also determined.

In all 3 trials in adults utilizing the recommended dosage regimen and outpatient use, the percentage of patients achieving headache response 4 hours after treatment, the primary outcome measure, was significantly greater among patients receiving AMERGE compared to those who received placebo. In all studies, response to 2.5 mg was numerically greater than response to 1 mg and in the largest of the three studies, there was a statistically significant greater percentage of patients with headache response at 4 hours in the 2.5 mg group compared to the 1 mg group. The results are summarized in Table 1.

**Table 1: Percentage of Adult Patients With Headache Response (Mild or No Headache) 4 Hours Following Treatment**

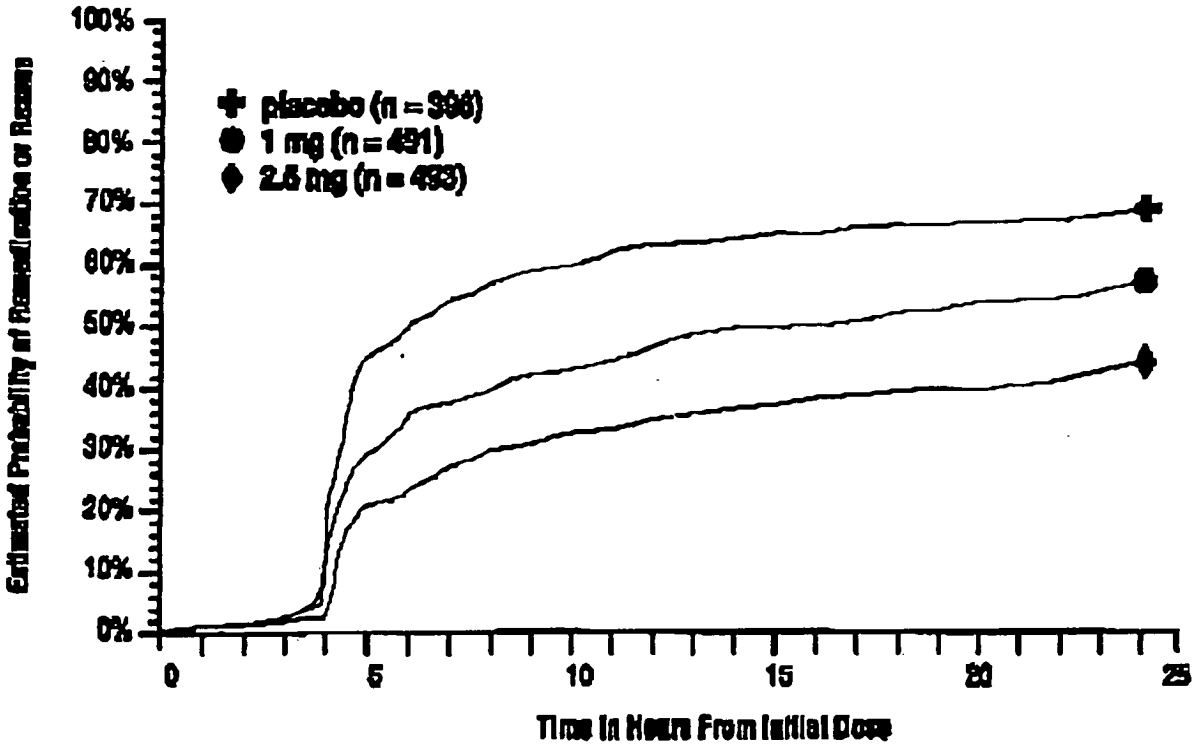
| | Placebo | AMERGE 1.0 mg | AMERGE 2.5 mg |
|---|---|---|---|
| Study 1 | 34% (n=122) | 50%* (n=117) | 60%* (n=127) |
| Study 2 | 27% (n=104) | 52%* (n=208) | 66%*# (n=199) |
| Study 3 | 32% (n=169) | 54%* (n=166) | 65%* (n=167) |

* $p<0.05$ in comparison with placebo.
# $p<0.05$ in comparison with 1 mg

In the single study in adolescents, there were no statistically significant differences between any of the treatment groups. The headache response rates at 4 hours (n) were 65% (n=74), 67% (n=78) and 64% (n=70) for the placebo, 1 mg and 2.5 mg groups, respectively.

**Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.**

The estimated probability of achieving an initial headache response in adults over the 4 hours following treatment is depicted in Figure 1.




*Kaplan-Meier plot based on data obtained in the three controlled clinical trials (studies 1, 2 and 3) providing evidence of efficacy with patients not using additional treatments censored at 24 hours. The plot also includes patients who had no response to the initial dose. Remedication was discouraged prior to 4 hours postdose.

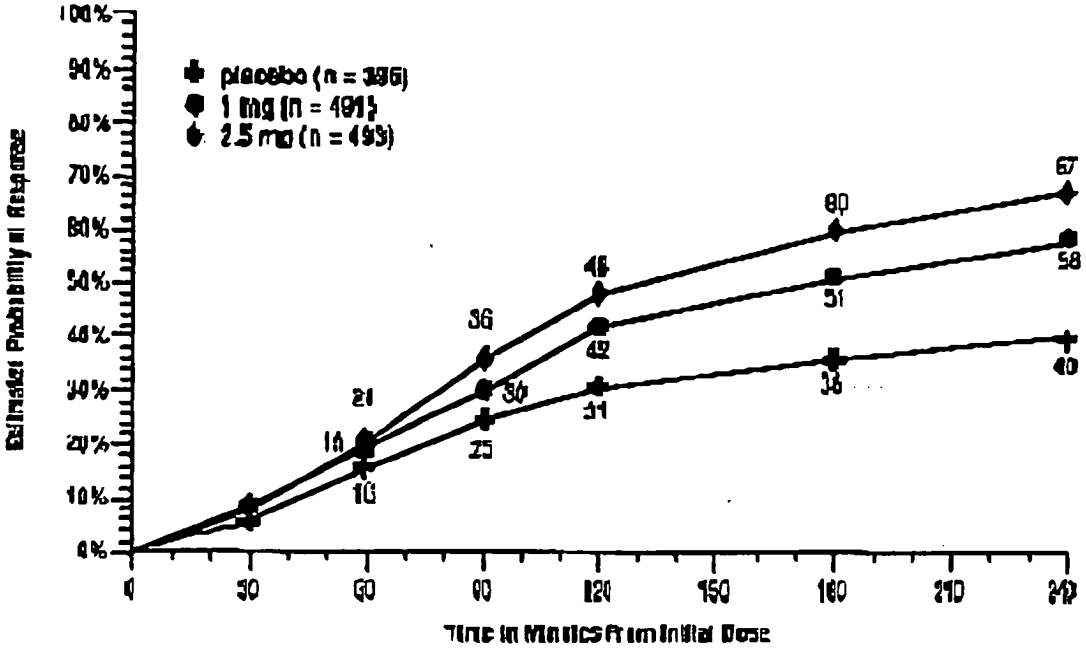
There is no evidence that doses of 5 mg provide a greater effect than 2.5 mg. There was no evidence to suggest that treatment with AMERGE was associated with an increase in the severity or frequency of migraine attacks. The efficacy of AMERGE Tablets was unaffected by presence of aura; gender, age, or weight of the patient; oral contraceptive use; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There were insufficient data to assess the impact of race on efficacy.

**INDICATIONS AND USAGE:** AMERGE Tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.

AMERGE Tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of AMERGE Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

**CONTRAINDICATIONS: AMERGE should not be given to patients with history, symptoms or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular disease should not receive AMERGE Tablets. Ischemic cardiac syndromes include, but are not limited to angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic**

**Figure 1: Estimated Probability of Achieving Initial Headache Response Within 4 Hours***




*The figure shows the probability over time of obtaining headache response (no or mild pain) following treatment with naratriptan tablets. The averages displayed are based on pooled data from the three controlled clinical trials providing evidence of efficacy (studies 1, 2 and 3). In this Kaplan-Meier plot, patients not achieving response within 240 minutes were censored at 240 minutes.

For patients with migraine associated nausea, photophobia, and phonophobia at baseline, there was a lower incidence of these symptoms 4 hours following administration of 1 and 2.5 mg AMERGE Tablets compared to placebo.

Four to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

**Figure 2: Estimated Probability of Patients Taking a Second Dose of AMERGE Tablets or Other Medication for Migraine Over the 24 Hours Following the Initial Dose of Study Treatment***

**It is recommended that patients who are intermittent long-term users of 5-HT1 agonists, including AMERGE Tablets, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use AMERGE Tablets.**

**The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to naratriptan.**

**Cardiac Events and Fatalities Associated With 5-HT1 Agonists:** Naratriptan can cause coronary artery vasospasm (see CLINICAL PHARMACOLOGY). Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT1 agonists. Considering the extent of use of 5-HT1 agonists in patients with migraine, the incidence of these events is extremely low.

***Premarketing Experience With AMERGE Tablets:*** Among approximately 3500 patients with migraine who participated in premarketing clinical trials of naratriptan tablets, four patients, treated with a single oral doses of naratriptan ranging from 1 to 10 mg experienced asymptomatic ischemic ECG changes with at least one, who took 7.5 mg, likely due to coronary vasospasm.

**Cerebrovascular Events and Fatalities With 5HT1 Agonists:** Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

**Other Vasospasm-Related Events:** 5HT1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5HT1 agonists.

**Increase in Blood Pressure:** In healthy volunteers, dose related increases in systemic blood pressure have been observed after administration of up to 20 mg of oral naratriptan. At the recommended doses, the elevations are generally small, although an increase of systolic pressure of 32 mm Hg was seen in one patient following a single 2.5 mg dose. The effect may be more pronounced in the elderly and hypertensive patients. A patient who was mildly hypertensive (the baseline blood pressure was 150/98) experienced a significant increase in blood pressure to 204/144 mm Hg 225 minutes after administration of a 10 mg oral dose. Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT1 agonists with and without a history of hypertension. Naratriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure and an 8% increase in mean aortic pressure was seen following dosing with 1.5 mg of subcutaneous naratriptan in a study evaluating 10 subjects with suspected CAD undergoing cardiac catheterization.

**Hypersensitivity:** Hypersensitivity (anaphylaxis/ anaphylactoid) reactions may occur in patients receiving naratriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

## PRECAUTIONS:

attacks. Peripheral vascular disease includes but is not limited to ischemic bowel disease (see WARNINGS).

Because AMERGE Tablets may increase blood pressure, they should not be given to patients with uncontrolled hypertension (see WARNINGS).

AMERGE Tablets are contraindicated in patients with severe renal impairment (creatinine clearance <15 mL/min) (see CLINICAL PHARMACOLOGY and DOSING AND ADMINISTRATION).

AMERGE Tablets are contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) (see CLINICAL PHARMACOLOGY and DOSING AND ADMINISTRATION).

AMERGE Tablets should not be administered to patients with hemiplegic or basilar migraine.

AMERGE Tablets should not be used within 24 hours of treatment with another 5 HT 1 agonist, an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

AMERGE Tablets are contraindicated in patients with hypersensitivity to naratriptan or any of the components.

WARNINGS: AMERGE Tablets should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Because of the potential of this class of compounds (5HT 1B/1D agonists) to cause coronary vasospasm, naratriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that 5HT1 agonists (including naratriptan) not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, naratriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of naratriptan take place in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following administration of AMERGE Tablets, in these patients with risk factors.

The administration of naratriptan with other 5-HT1 agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of naratriptan and other 5-HT1 agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5HT1 agonists. If concomitant treatment with naratriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

**Drug/Laboratory Test Interactions:** AMERGE Tablets are not known to interfere with commonly employed clinical laboratory tests.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** ***Carcinogenesis:*** Lifetime carcinogenicity studies, 104 weeks in duration, were carried out in mice and rats by oral gavage. There was no evidence of an increase in tumors related to naratriptan administration in mice receiving up to 200 mg/kg/day. That dose was associated with a plasma AUC exposure which was 110 times the exposure in humans receiving the maximum recommended daily dose of 5 mg. Two rat studies were conducted, one using a standard diet and the other a nitrite-supplemented diet (naratriptan can be nitrosated in vitro to form a mutagenic product that has been detected in the stomachs of rats fed a high nitrite diet). Doses of 5, 20, and 90 mg/kg were associated with week 13 AUC exposures that in the standard diet study were 7, 40, and 236 times, and in the nitrite-supplemented diet study were 7, 29, and 180 times the exposure attained in humans given the maximum recommended daily dose of 5 mg. In both studies there was an increase in the incidence of thyroid follicular hyperplasia in high dose males and females and in thyroid follicular adenomas in high dose males. In the standard diet study only, there was also an increase in the incidence of benign c-cell adenomas in the thyroid of high dose males and females. The exposures achieved at the no-effect dose for thyroid tumors were 40 (standard diet) and 29 (nitrite-supplemented diet) times the exposure achieved in humans receiving the maximum recommended daily dose of 5 mg. In the nitrite-supplemented diet study only, the incidence of benign lymphocytic thymoma was increased in all treated groups of females. It was not determined if the nitrosated product is systemically absorbed. However, no changes were seen in the stomachs of rats in that study.

***Mutagenesis:*** Naratriptan was not mutagenic when tested in two gene mutation assays, the Ames test and the in vitro thymidine locus mouse lymphoma assay. It was not clastogenic in two cytogenetics assays, the in vitro human lymphocyte assay and the in vivo mouse micronucleus assay. Naratriptan can be nitrosated in vitro to form a mutagenic product (WHO nitrosation assay) that has been detected in the stomachs of rats fed a nitrite-supplemented diet.

***Impairment of Fertility:*** In a reproductive toxicity study in which male and female rats were dosed prior to and throughout the mating period with 10, 60, 170, or 340 mg/kg/day (plasma exposures [AUC] approximately 11, 70, 230, and 470 times, respectively, the human exposure at the maximum recommended daily dose [MRDD] of 5 mg), there was a treatment-related decrease in the number of females exhibiting normal estrous cycles at doses of 170 mg/kg/day or greater and an increase in preimplantation loss at 60 mg/kg/day or greater. In high dose group males, testicular/epididymal atrophy accompanied by spermatozoa depletion reduced mating success and may have contributed to the observed preimplantation loss. The exposures achieved at the no-effect doses for preimplantation loss, anestrus, and testicular effects were approximately 11, 70, and 230 times, respectively, the exposures in humans receiving the MRDD.

In a study in which rats were dosed orally with 10, 60, or 340 mg/kg/day for 6 months, changes in the female reproductive tract including atrophic or cystic ovaries and anestrus were seen at the high dose. The exposure at the no-effect dose of 60 mg/kg was approximately 85 times the exposure in humans receiving the MRDD.

**General:** Chest discomfort (including pain, pressure, heaviness, tightness) has been reported after administration of 5-HT1 agonists, including AMERGE Tablets. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials with AMERGE Tablets. Because naratriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following naratriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of naratriptan, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following naratriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS).

AMERGE Tablets should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired renal or hepatic function (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION).

Care should be taken to exclude other potentially serious neurological conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient has no response to the first dose of naratriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

**Binding to Melanin-Containing Tissues:** In rats treated with a single oral dose (10 mg/kg) of radiolabeled naratriptan, the elimination half-life of radioactivity from the eye was 90 days, suggesting that naratriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that naratriptan could cause toxicity in these tissues after extended use. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long term ophthalmologic effects.

**Changes in the Precorneal Tear Film:** Dogs receiving oral naratriptan showed transient changes in the precorneal tear film. Corneal stippling was seen at the lowest dose tested, 1 mg/kg per day, and occurred intermittently from day 1 throughout the first 2 to 3 weeks of treatment. Although a no-effect dose was not established the exposure at the lowest dose tested was approximately five times the human exposure after a 5 mg oral dose.

**Information for Patients:** See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

**Laboratory Tests:** No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with AMERGE Tablets.

**Drug Interactions:** Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and naratriptan within 24 hours is contraindicated(see CONTRAINDICATIONS).

**Geriatric Use:** The use of naratriptan in elderly patients is not recommended.

AMERGE Tablets are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in elderly patients who have reduced renal function. In addition, elderly patients are more likely to have decreased hepatic function; they are at higher risk for CAD; and blood pressure increases may be more pronounced in the elderly. Clinical studies of AMERGE Tablets did not include patients over 65 years of age.

**ADVERSE REACTIONS: Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).**

**Incidence in Controlled Clinical Trials:** The most common adverse event was malaise/fatigue, which occurred at a rate of 3% and at least two times placebo rate. Since patients treated only one to three headaches in the controlled clinical trials, the opportunity for discontinuation of therapy in response to an adverse event was limited. In a long term, open label study where patients where allowed to treat multiple migraine attacks for up to 1 year, 15 patients (3.6%) discontinued treatment due to adverse events.

Table 2 lists adverse events that occurred in five placebo controlled clinical trials of approximately 1752 exposures to placebo and AMERGE Tablets in adult migraine patients. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Only events that occurred at a frequency of 1% or more in the AMERGE Tablets 2.5 mg treatment group and were more frequent in that group than in the placebo group are included in Table 2. From this table, it appears that many of these adverse events are dose related.

**Table 2: Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in Placebo-Controlled Migraine Trials**

| Adverse Event Type | Placebo (n=498) | AMERGE 1 mg (n= 627) | AMERGE 2.5 mg (n= 627) |
|---|---|---|---|
| Atypical Sensation | 1% | 2% | 4% |
| Paresthesias (all types) | < 1% | 1% | 2% |
| | | | |
| Gastrointestinal | 5% | 6% | 7% |
| Nausea | 4% | 4% | 5% |
| | | | |
| Neurological | 3% | 4% | 7% |
| Dizziness | 1% | 1% | 2% |
| Drowsiness | < 1% | 1% | 2% |
| Malaise/fatigue | 1% | 2% | 2% |
| | | | |
| Pain and Pressure sensation | 2% | 2% | 4% |
| Throat/neck symptoms | 1% | 1% | 2% |

One event present in more than 1% of patients receiving AMERGE Tablets (vomiting) occurred more frequently on placebo than on naratriptan 2.5 mg.

**Pregnancy:** Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women; therefore, naratriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

To monitor fetal outcomes of pregnant women exposed to AMERGE, Glaxo Wellcome Inc. maintains a Naratriptan Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 722-9292, ext. 39441.

In reproductive toxicity studies in rats and rabbits, oral administration of naratriptan was associated with developmental toxicity (embryolethality, fetal abnormalities, pup mortality, offspring growth retardation) at doses producing maternal plasma drug exposures as low as 11 and 2.5 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 5 mg.

When pregnant rats were administered naratriptan during the period of organogenesis at doses of 10, 60 or 340 mg/kg/day, there was a dose-related increase in embryonic death, with a statistically significant difference at the highest dose, and incidences of fetal structural variations (incomplete/irregular ossification of skull bones, sternebrae, ribs) were increased at all doses. The maternal plasma exposures (AUC) at these doses were approximately 11, 70, and 470 times the exposure in humans at the MRDD. The high dose was maternally toxic, as evidenced by decreased maternal body weight gain during gestation. A no-effect dose for developmental toxicity in rats exposed during organogenesis was not established.

When doses of 1, 5, or 30 mg/kg/day were given to pregnant Dutch rabbits throughout organogenesis, the incidence of a specific fetal skeletal malformation (fused sternebrae) was increased at the high dose, and increased incidences of embryonic death and fetal variations (major blood vessel variations, supernumerary ribs, incomplete skeletal ossification) were observed at all doses (4, 20, and 120 times, respectively, the MRDD on a body surface area basis). Maternal toxicity (decreased body weight gain) was evident at the high dose in this study. In a similar study in New Zealand White rabbits (1, 5, or 30 mg/kg/day throughout organogenesis), decreased fetal weights and increased incidences of fetal skeletal variations were observed at all doses (maternal exposures equivalent to 2.5, 19, and 140 times exposure in humans receiving the MRDD), while maternal body weight gain was reduced at 5 mg/kg or greater. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was not established.

When female rats were treated with 10, 60, or 340 mg/kg/day during late gestation and lactation, offspring behavioral impairment (tremors) and decreased offspring viability and growth were observed at doses of 60 mg/kg or greater, while maternal toxicity occurred only at the highest dose. Maternal exposures at the no-effect dose for developmental effects in this study were approximately 11 times the exposure in humans receiving the MRDD.

**Nursing Mothers:** Naratriptan related material is excreted in the milk of rats. Therefore, caution should be exercised when considering the administration of AMERGE Tablets to a nursing woman.

**Pediatric Use:** Safety and effectiveness of AMERGE Tablets in pediatric patients (less than 18 years of age) have not been established.

One randomized, placebo controlled clinical trial evaluating oral naratriptan (0.25 to 2.5 mg) in pediatric patients aged 12 to 17 years evaluated a total of 300 adolescent migraineurs. This study did not establish the efficacy of oral naratriptan compared to placebo in the treatment of migraine in adolescents (see CLINICAL TRIALS). Adverse events observed in this clinical trial were similar in nature to those reported in clinical trials in adults.

***Musculoskeletal:*** Infrequent were muscle pain, arthralgia and articular rheumatism, muscle cramps and spasms, joint and muscle stiffness, tightness and rigidity. Rare were bone and skeletal pain.

***Neurological:*** Frequent was vertigo. Infrequent were tremors, cognitive function disorders, sleep disorders, and disorders of equilibrium. Rare were compressed nerve syndromes, confusion, sedation, hyperesthesia, coordination disorders, paralysis of cranial nerves, decreased consciousness, dreams, altered sense of taste, neuralgia, neuritis, aphasia, hypoesthesia, motor retardation, muscle twitching and fasciculation, psychomotor restlessness, and convulsions.

***Non-Site Specific:*** Infrequent were chills and/or fever, descriptions of odor or taste, edema and swelling, allergies, and allergic reactions. Rare were spasms and mobility disorders.

***Pain and Pressure Sensations:*** Frequent were pressure/tightness/heaviness sensations.

***Psychiatry:*** Infrequent were anxiety, depressive disorders and detachment. Rare were aggression and hostility, agitation, hallucinations, panic, and hyperactivity.

***Reproduction:*** Rare were lumps of female reproductive tract, breast inflammation, inflammation of vagina, inflammation of fallopian tube, breast discharge, endometrium disorders, decreased libido and lumps of breast.

***Skin:*** Infrequent were sweating, skin rashes, pruritus, and urticaria. Rare were skin erythema, dermatitis and dermatosis, hair loss and alopecia, pruritic skin rashes, acne and folliculitis, allergic skin reactions, macular skin/rashes, skin photosensitivity, photodermatitis, skin flakiness, and dry skin.

***Urology:*** Infrequent were bladder inflammation and polyuria and diuresis. Rare were urinary tract hemorrhage, urinary urgency, pyelitis, and urinary incontinence.

**DRUG ABUSE AND DEPENDENCE:** In one clinical study enrolling 12 subjects, all of whom had experience using oral opiates and other psychoactive drugs, AMERGE Tablets produced less intense subjective responses ordinarily associated with many drugs of abuse than did codeine (30 to 90 mg).

**OVERDOSAGE:** A patient who was mildly hypertensive experienced a significant increase in blood pressure after administration of a 10-mg dose starting at 30 minutes (baseline value of 150/98 to 204/144 mm Hg at 225 minutes). This event resolved after treatment with antihypertensive therapy. Oral administration of 25 mg of naratriptan in one healthy young male subject increased blood pressure from 120/67 mm Hg pretreatment up to 191/113 mm Hg at approximately 6 hours postdose and resulted in adverse events including lightheadedness, tension in the neck, tiredness, and loss of coordination. Blood pressure returned to near baseline by 8 hours after dosing without any pharmacological intervention.

Another subject experienced asymptomatic ischemic ECG changes likely due to coronary artery vasospasm approximately 2 hours following a 7.5 mg oral dose.

The elimination half-life of naratriptan is about 6 hours (see CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with AMERGE Tablets should continue for at least 24 hours or while symptoms or signs persist. There is no specific antidote to naratriptan. Standard supportive treatment should be applied as required. If the patient presents with chest pain or other symptoms consistent with angina pectoris, ECG monitoring should be performed for evidence of

AMERGE Tablets are generally well tolerated. Most adverse reactions were mild and transient.

The incidence of adverse events in placebo controlled clinical trials was not affected by age or weight of the patients, duration of headache prior to treatment, presence of aura, use of prophylactic medications, or tobacco use. There were insufficient data to assess the impact of race on the incidence of adverse events.

**Other Events Observed in Association With the Administration of AMERGE Tablets:** In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of AMERGE Tablets in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc. limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n=3557) exposed to oral naratriptan doses up to 10 mg. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those occurring in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1000 patients, and rare adverse events are those occurring in fewer than 1/1000 patients.

***Atypical sensations :*** Frequent were warm/cold temperature sensations. Infrequent were feeling strange and burning/stinging sensation.

***Cardiovascular:*** Infrequent were palpitations, increased blood pressure, tachyarrhythmias, and abnormal ECG (PR prolongation, $QT_c$ prolongation, ST/T wave abnormalities, premature ventricular contractions, atrial flutter, or atrial fibrillation), and syncope. Rare were bradycardia, varicosities, hypotension, and heart murmurs.

***Ear, Nose, and Throat:*** Frequent were ear, nose and throat infections. Infrequent were phonophobia, sinusitis, upper respiratory inflammation and tinnitus. Rare were allergic rhinitis, labyrinthitis, ear, nose and throat hemorrhage and hearing difficulty.

***Endocrine and Metabolic:*** Infrequent were thirst and polydipsia, dehydration and fluid retention. Rare were hyperlipidemia, hypercholesterolemia, hypothyroidism, hyperglycemia, glycosuria and ketonuria,.

***Eye:*** Frequent was photophobia. Infrequent was blurred vision. Rare were eye pain and discomfort, sensation of eye pressure, eye hemorrhage, dry eyes, difficulty focusing and scotoma.

***Gastrointestinal:*** Frequent were hyposalivation and vomiting. Infrequent were dyspeptic symptoms, diarrhea, gastrointestinal discomfort and pain, gastroenteritis, and constipation. Rare were abnormal liver function tests, abnormal bilirubin levels, hemorrhoids, gastritis, esophagitis, salivary gland inflammation, oral itching and irritation, regurgitation and reflux and gastric ulcers.

***Hematological Disorders:*** Infrequent was increased white cells. Rare were thrombocytopenia. quantitative red cell or hemoglobin defects, anemia, and purpura.

***Lower Respiratory Tract:*** Infrequent were bronchitis, cough and pneumonia. Rare were tracheitis, asthma, pleuritis, and airway constriction and obstruction.

ischemia. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of naratriptan.

**DOSAGE AND ADMINISTRATION:** In controlled clinical trials, single doses of 1 mg and 2.5 mg of AMERGE Tablets taken with fluid were effective for the acute treatment of migraines in adults. A greater proportion of patients had headache response following a 2.5 mg dose than following a 1 mg dose (see CLINICAL TRIALS). Individuals may vary in response to doses of AMERGE Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 2.5 mg dose with the potential for a greater risk of adverse events. If the headache returns or if the patient has only partial response, the dose may be repeated once after 4 hours, for a maximum dose of 5 mg in a 24 hour period. There is evidence that doses of 5 mg do not provide a greater effect than 2.5 mg.

The safety of treating, on average, more than four headaches in a 30 day period has not been established.

**Renal impairment:** The use of AMERGE is contraindicated in patients with severe renal impairment (creatinine clearance <15 mL/min) because of decreased clearance of the drug. (See CONTRAINDICATIONS and CLINICAL PHARMACOLOGY). In patients with mild to moderate renal impairment, the maximum daily dose should not exceed 2.5 mg over a 24 hour period and a lower starting dose should be considered.

**Hepatic impairment:** The use of AMERGE is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) because of decreased clearance (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY). In patients with mild or moderate hepatic impairment, the maximum single dose should not exceed 2.5 mg over a 24 hour period and a lower starting dose should be considered (see CLINICAL PHARMACOLOGY).

**HOW SUPPLIED:** AMERGE Tablets, 1 and 2.5 mg of naratriptan (base) as the hydrochloride. AMERGE Tablets, 1 mg, are white, D-shaped, film-coated tablets embossed with "GX CE3" on one side in blister packs of 9 tablets (NDC 0173-0561-00) and in bottles of 30 tablets (NDC 0173-0561-02). AMERGE Tablets, 2.5 mg, are green, D-shaped, film-coated tablets embossed with "GX CE5" on one side in blister packs of 9 tablets (NDC 0173-0562-00) and in bottles of 30 tablets (NDC 0173-0562-02).

**Store at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP).**

**PATIENT INFORMATION:** The following wording is contained in a separate leaflet provided for patients.

**Information for the Patient**
**AMERGE™ (naratriptan hydrochloride) Tablets**

Please read this leaflet carefully before you take AMERGE Tablets. This leaflet provides a summary of the information available about your medicine. Please do not throw away this leaflet until you have finished your medicine. You may need to read this leaflet again. This leaflet does not contain all the information on AMERGE Tablets. For further information or advice, ask your doctor or pharmacist.

**Information About Your Medicine:**

The name of your medicine is AMERGE (naratriptan hydrochloride) Tablets. It can be obtained only by prescription from your doctor. The decision to use AMERGE Tablets is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40), you should tell your doctor, who should evaluate you for heart disease in order to determine if AMERGE is appropriate for you. The majority of those who have taken AMERGE Tablets have not experienced any significant side effects. Rarely, deaths and/or serious heart problems have been reported with this class of medicines; in all but a few instances, however, these deaths and/or serious heart problems occurred in people with heart disease and it was not clear whether these medications were a contributing factor.

***1. The Purpose of Your Medicine:***

AMERGE Tablets are intended to relieve your migraine, but not to prevent or reduce the number of attacks you experience. Use AMERGE Tablets only to treat an actual migraine attack.

***2. Important Questions to Consider Before Taking AMERGE Tablets:***

If the answer to any of the following questions is YES or if you do not know the answer, then please discuss it with your doctor before you use AMERGE Tablets.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you not using adequate contraception? Are you breast-feeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medication because of an allergy or other problems?
- Are you taking any other migraine medications, including other 5-HT1 agonists such as IMITREX® (sumatriptan), or medications containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medication for depression such as selective serotonin reuptake inhibitors [SSRIs])?
- Have you had, or do you have, any disease of the kidney or liver?
- Is this headache different from your usual migraine attacks?

Remember, if you answered YES to any of the above questions, then discuss it with your doctor.

***3. The Use of AMERGE Tablets During Pregnancy:***

Do not use AMERGE Tablets if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

***4. How to Use AMERGE Tablets:***

For adults, the usual dose is a single tablet taken whole with fluids. It may be given at any time after the headache starts. For an individual attack, if you have no response to the first tablet, do not take a second tablet without first talking to your doctor. If you need more relief due to a partial response or return of your headache after the first tablet, a second tablet may be taken but not sooner than 4 hours following the first tablet. Do not take more than a total of two AMERGE Tablets in any 24 hour period. If you have kidney or liver disease, take as directed by your doctor.

***5. Side Effects to Watch for:***

- Some patients experience pain or tightness in the chest or throat when using AMERGE Tablets. If this happens to you, then discuss it with your doctor before using any more AMERGE Tablets. If the chest pain, tightness or pressure is severe or does not go away, call your doctor immediately.

- Shortness of breath; wheeziness; heart throbbing, swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor immediately. Do not take any more AMERGE Tablets unless your doctor tells you to do so.
- Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with AMERGE Tablets. A few people may feel drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.
- If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

***6. What to Do if an Overdose is Taken:***

If you have taken more medication than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately.

***7. Storing Your Medicine:***

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Store your medication away from heat and light. Do not store at temperatures above 77°F (25°C). If your medication has expired (the expiration date is printed on the treatment pack), throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
Made in England

U.S. Patent No. 4,997,841


January 1998 (RL no.) (item no)

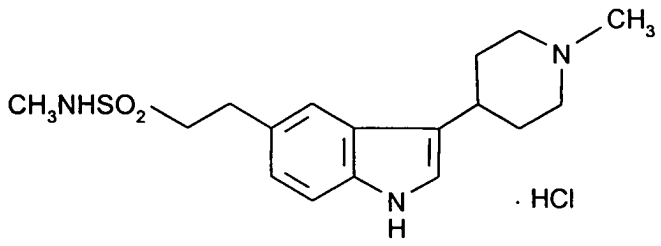
# EXHIBIT 4

Product Information / Package Insert
for
AMERGE™(naratriptan hydrochloride) Tablets

NDA 20-763

# AMERGE™
## (naratriptan hydrochloride)
## Tablets

**DESCRIPTION:** AMERGE Tablets contain naratriptan as the hydrochloride, which is a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Naratriptan hydrochloride is chemically designated as N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride, and it has the following structure:




The empirical formula is $C_{17}H_{25}N_3O_2S$•HCl, representing a molecular weight of 371.93. Naratriptan hydrochloride is a white to pale yellow powder that is readily soluble in water. Each AMERGE Tablet for oral administration contains 1.11 or 2.78 mg of naratriptan hydrochloride equivalent to 1 or 2.5 mg of naratriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium; hydroxypropyl methylcellulose; lactose; magnesium stearate; microcrystalline cellulose; triacetin; and titanium dioxide, iron oxide yellow, and indigo carmine aluminum lake (FD&C Blue No. 2) for coloring.

**CLINICAL PHARMACOLOGY:**

**Mechanism of Action:** Naratriptan binds with high affinity to 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors and has no significant affinity or pharmacological activity at 5-HT$_{2-4}$ receptor subtypes or at adrenergic $\alpha_1$, $\alpha_2$, or $\beta$; dopaminergic $D_1$ or $D_2$; muscarinic; or benzodiazepine receptors.

The therapeutic activity of naratriptan in migraine is generally attributed to its agonist activity at 5-HT$_{1D/1B}$ receptors. Two current theories have been proposed to explain the efficacy of 5-HT$_{1D/1B}$ receptor agonists in migraine. One theory suggests that activation of 5-HT$_{1D/1B}$ receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-HT$_{1D/1B}$ receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.

In the anesthetized dog, naratriptan has been shown to reduce the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. While the effect on blood flow was selective for the carotid arterial bed, increases in vascular resistance of up to 30% were seen in the coronary arterial bed. Naratriptan has also been shown to inhibit trigeminal nerve activity in rat and cat. In 10 human subjects with suspected coronary artery disease (CAD) undergoing coronary artery catheterization, there was a 1% to 10% reduction in coronary artery diameter following subcutaneous injection of 1.5 mg of naratriptan.

**Pharmacokinetics:** Naratriptan tablets are well absorbed, with about 70% oral bioavailability. Following administration of a 2.5-mg tablet orally, the peak concentrations are obtained in 2 to 3 hours. After administration of 1- or 2.5-mg tablets, the $C_{max}$ is somewhat (about 50%) higher in women (not corrected for mg/kg dose) than in men. During a migraine attack, absorption was slower, with a $t_{max}$ of 3 to 4 hours. Food

does not affect the pharmacokinetics of naratriptan. Naratriptan displays linear kinetics over the therapeutic dose range.

The steady-state volume of distribution of naratriptan is 170 L. Plasma protein binding is 28% to 31% over the concentration range of 50 to 1000 ng/mL.

Naratriptan is predominantly eliminated in urine, with 50% of the dose recovered unchanged and 30% as metabolites in urine. In vitro, naratriptan is metabolized by a wide range of cytochrome P450 isoenzymes into a number of inactive metabolites.

The mean elimination half-life of naratriptan is 6 hours. The systemic clearance of naratriptan is 6.6 mL/min/kg. The renal clearance (220 mL/min) exceeds glomerular filtration rate, indicating active tubular secretion. Repeat administration of naratriptan tablets does not result in drug accumulation.

**Special Populations:** ***Age:*** A small decrease in clearance (approximately 26%) was observed in healthy elderly subjects (65 to 77 years) compared to younger patients, resulting in slightly higher exposure (see PRECAUTIONS).

***Race:*** The effect of race on the pharmacokinetics of naratriptan has not been examined.

***Renal Impairment:*** Clearance of naratriptan was reduced by 50% in patients with moderate renal impairment (creatinine clearance 18 to 39 mL/min) compared to the normal group. Decrease in clearances resulted in an increase of mean half-life from 6 hours (healthy) to 11 hours (range: 7 to 20 hours). The mean $C_{max}$ increased by approximately 40%. The effects of severe renal impairment (creatinine clearance ≤15 mL/min) on the pharmacokinetics of naratriptan has not been assessed. (See CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION.)

***Hepatic Impairment:*** Clearance of naratriptan was decreased by 30% in patients with moderate hepatic impairment (Child-Pugh grade A or B). This resulted in an approximately 40% increase in the half-life (range: 8 to 16 hours). The effects of severe hepatic impairment (Child-Pugh grade C) on the pharmacokinetics of naratriptan have not been assessed. (See CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION.)

**Drug Interactions:** In normal volunteers, coadministration of single doses of naratriptan tablets and alcohol did not result in substantial modification of naratriptan pharmacokinetic parameters.

From population pharmacokinetic analyses, coadministration of naratriptan and fluoxetine, beta-blockers, or tricyclic antidepressants did not affect the clearance of naratriptan.

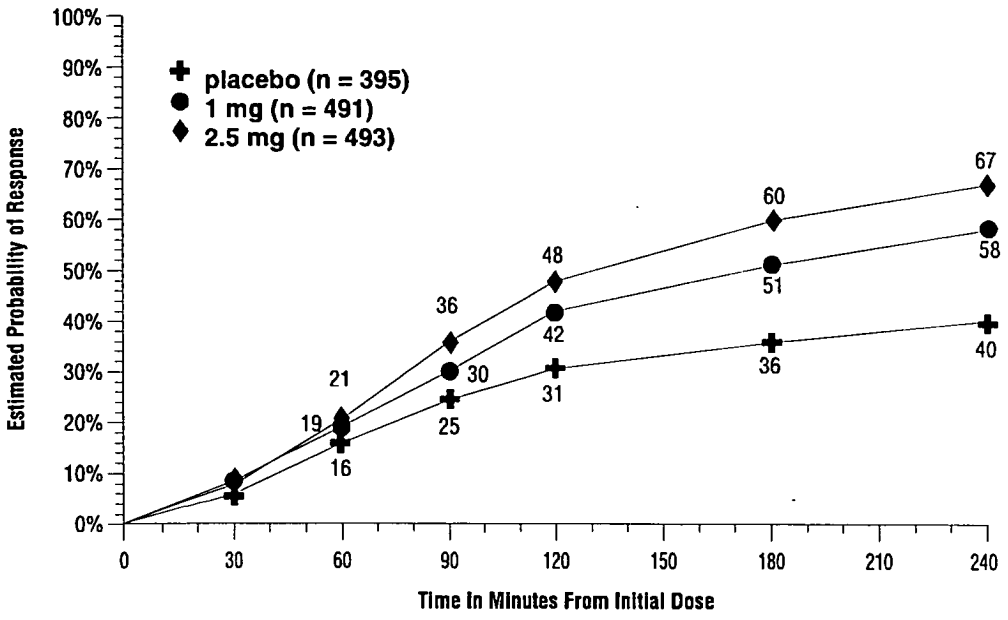
Naratriptan does not inhibit monoamine oxidase (MAO) enzymes and is a poor inhibitor of P450; metabolic interactions between naratriptan and drugs metabolized by P450 or MAO are therefore unlikely.

***Oral Contraceptives:*** Oral contraceptives reduced clearance by 32% and volume of distribution by 22%, resulting in slightly higher concentrations of naratriptan. Hormone replacement therapy had no effect on pharmacokinetics in older female patients.

Smoking increased the clearance of naratriptan by 30%.

**CLINICAL TRIALS:** The efficacy of AMERGE Tablets in the acute treatment of migraine headaches was evaluated in six randomized, double-blind, placebo-controlled studies of which 4 used the recommended dosing regimen and were conducted as outpatient trials. Three of these studies enrolled adult patients who were predominantly female (86%) and Caucasian (96%) with a mean age of 41 (range: 18 to 65). One study enrolled adolescents with a mean age of 14 (range: 12 to 17). In the adolescent study, 54% of the patients were female and 89% were Caucasian. In all studies, patients were instructed to treat at least one moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 4 hours after dosing. Associated symptoms such as nausea, vomiting, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of AMERGE Tablets or other medication was allowed

**Figure 1: Estimated Probability of Achieving Initial Headache Response Within 4 Hours***




*The figure shows the probability over time of obtaining headache response (no or mild pain) following treatment with naratriptan tablets. The averages displayed are based on pooled data from the three controlled clinical trials providing evidence of efficacy (Studies 1, 2, and 3). In this Kaplan-Meier plot, patients not achieving response within 240 minutes were censored at 240 minutes.

For patients with migraine-associated nausea, photophobia, and phonophobia at baseline, there was a lower incidence of these symptoms 4 hours following administration of 1- and 2.5-mg AMERGE Tablets compared to placebo.

Four to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

4 to 24 hours after the initial treatment for recurrent headache. The frequency and time to use of these additional treatments were also determined.

In all 3 trials in adults utilizing the recommended dosage regimen and outpatient use, the percentage of patients achieving headache response 4 hours after treatment, the primary outcome measure, was significantly greater among patients receiving AMERGE compared to those who received placebo. In all studies, response to 2.5 mg was numerically greater than response to 1 mg and in the largest of the three studies, there was a statistically significant greater percentage of patients with headache response at 4 hours in the 2.5-mg group compared to the 1-mg group. The results are summarized in Table 1.

**Table 1: Percentage of Adult Patients With Headache Response (Mild or No Headache) 4 Hours Following Treatment**

| | Placebo | AMERGE 1.0 mg | AMERGE 2.5 mg |
|---|---|---|---|
| Study 1 | 34% (n = 122) | 50%* (n = 117) | 60%* (n = 127) |
| Study 2 | 27% (n = 104) | 52%* (n = 208) | 66%*† (n = 199) |
| Study 3 | 32% (n = 169) | 54%* (n = 166) | 65%* (n = 167) |

* $P<0.05$ in comparison with placebo.

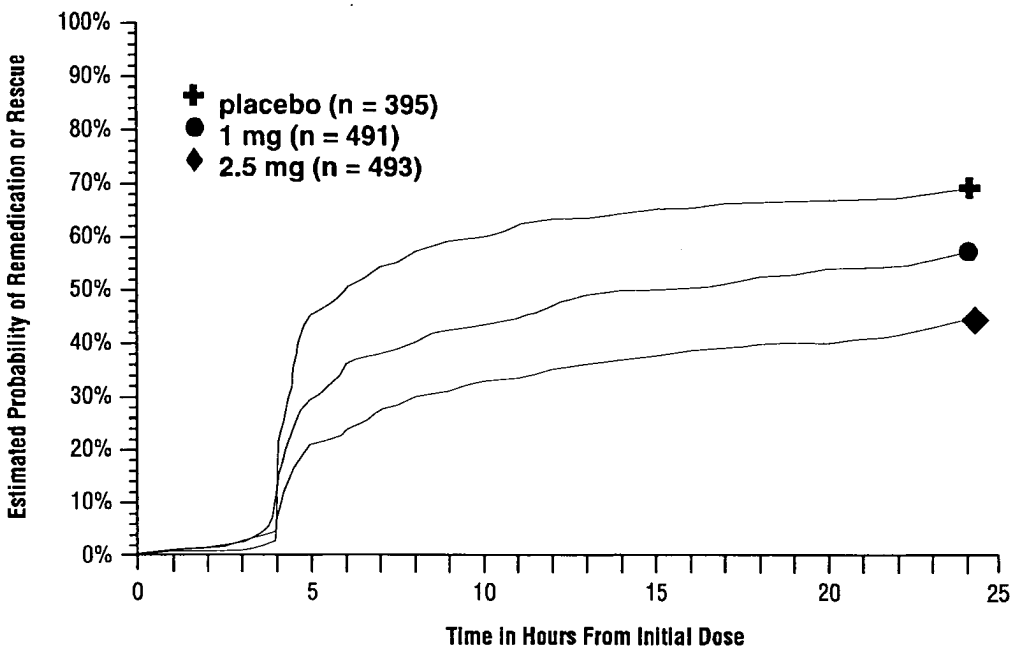
† $P<0.05$ in comparison with 1 mg.

In the single study in adolescents, there were no statistically significant differences between any of the treatment groups. The headache response rates at 4 hours (n) were 65% (n = 74), 67% (n = 78), and 64% (n = 70) for placebo, 1-mg, and 2.5-mg groups, respectively.

**Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.**

The estimated probability of achieving an initial headache response in adults over the 4 hours following treatment is depicted in Figure 1.

**Figure 2: Estimated Probability of Patients Taking a Second Dose of AMERGE Tablets or Other Medication for Migraine Over the 24 Hours Following the Initial Dose of Study Treatment***




*Kaplan-Meier plot based on data obtained in the three controlled clinical trials (Studies 1, 2, and 3) providing evidence of efficacy with patients not using additional treatments censored at 24 hours. The plot also includes patients who had no response to the initial dose. Remedication was discouraged prior to 4 hours postdose.

There is no evidence that doses of 5 mg provide a greater effect than 2.5 mg. There was no evidence to suggest that treatment with AMERGE was associated with an increase in the severity or frequency of migraine attacks. The efficacy of AMERGE Tablets was unaffected by presence of aura; gender, age, or weight of the patient; oral contraceptive use; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There was insufficient data to assess the impact of race on efficacy.

**INDICATIONS AND USAGE:** AMERGE Tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.

AMERGE Tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of AMERGE Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

**CONTRAINDICATIONS: AMERGE Tablets should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive AMERGE Tablets. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of**

myocardial infarction, and silent myocardial ischemia. Cerebrovascular sydromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because AMERGE Tablets may increase blood pressure, they should not be given to patients with uncontrolled hypertension (see WARNINGS).

AMERGE Tablets are contraindicated in patients with severe renal impairment (creatinine clearance <15 mL/min) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

AMERGE Tablets are contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

AMERGE Tablets should not be administered to patients with hemiplegic or basilar migraine.

AMERGE Tablets should not be used within 24 hours of treatment with another 5-$HT_1$ agonist, an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

AMERGE Tablets are contraindicated in patients with hypersensitivity to naratriptan or any of the components.

WARNINGS: AMERGE Tablets should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, naratriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that 5-$HT_1$ agonists (including naratriptan) not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic, or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, naratriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of naratriptan take place in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following administration of AMERGE Tablets, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of 5-$HT_1$ agonists, including AMERGE Tablets, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use AMERGE Tablets.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to naratriptan.

Cardiac Events and Fatalities Associated With 5-$HT_1$ Agonists: Naratriptan can cause coronary artery vasospasm (see CLINICAL PHARMACOLOGY). Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours

AMERGE Tablets should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired renal or hepatic function (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION).

Care should be taken to exclude other potentially serious neurological conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-$HT_1$ agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient has no response to the first dose of naratriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

**Binding to Melanin-Containing Tissues:** In rats treated with a single oral dose (10 mg/kg) of radiolabeled naratriptan, the elimination half-life of radioactivity from the eye was 90 days, suggesting that naratriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin-rich tissues over time, this raises the possibility that naratriptan could cause toxicity in these tissues after extended use. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

**Changes in the Precorneal Tear Film:** Dogs receiving oral naratriptan showed transient changes in the precorneal tear film. Corneal stippling was seen at the lowest dose tested, 1 mg/kg per day, and occurred intermittently from day 1 throughout the first 2 to 3 weeks of treatment. Although a no-effect dose was not established, the exposure at the lowest dose tested was approximately five times the human exposure after a 5-mg oral dose.

**Information for Patients:** See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

**Laboratory Tests:** No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with AMERGE Tablets.

**Drug Interactions:** Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and naratriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

The administration of naratriptan with other 5-$HT_1$ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of naratriptan and other 5-$HT_1$ agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-$HT_1$ agonists. If concomitant treatment with naratriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

**Drug/Laboratory Test Interactions:** AMERGE Tablets are not known to interfere with commonly employed clinical laboratory tests.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** ***Carcinogenesis:*** Lifetime carcinogenicity studies, 104 weeks in duration, were carried out in mice and rats by oral gavage. There was no evidence of an increase in tumors related to naratriptan administration in mice receiving up to 200 mg/kg/day. That dose was associated with a plasma AUC exposure that was 110 times the exposure in humans receiving the maximum recommended daily dose of 5 mg. Two rat studies were conducted, one using a standard diet and the other a nitrite-supplemented diet (naratriptan can be nitrosated in vitro to form a mutagenic product that has been detected in the stomachs of rats fed a high nitrite diet). Doses of 5, 20, and 90 mg/kg were associated with week 13 AUC exposures that in the standard diet study were 7, 40, and 236 times, and in the

following the administration of 5-$HT_1$ agonists. Considering the extent of use of 5-$HT_1$ agonists in patients with migraine, the incidence of these events is extremely low.

***Premarketing Experience With AMERGE Tablets:*** Among approximately 3500 patients with migraine who participated in premarketing clinical trials of naratriptan tablets, four patients treated with single oral doses of naratriptan ranging from 1 to 10 mg experienced asymptomatic ischemic ECG changes with at least one, who took 7.5 mg, likely due to coronary vasospasm.

**Cerebrovascular Events and Fatalities With 5-$HT_1$ Agonists:** Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-$HT_1$ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

**Other Vasospasm-Related Events:** 5-$HT_1$ agonists may cause vasospastic reactions other than coronary artery spasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-$HT_1$ agonists.

**Increase in Blood Pressure:** In healthy volunteers, dose-related increases in systemic blood pressure have been observed after administration of up to 20 mg of oral naratriptan. At the recommended doses, the elevations are generally small, although an increase of systolic pressure of 32 mmHg was seen in one patient following a single 2.5-mg dose. The effect may be more pronounced in the elderly and hypertensive patients. A patient who was mildly hypertensive (the baseline blood pressure was 150/98) experienced a significant increase in blood pressure to 204/144 mmHg 225 minutes after administration of a 10-mg oral dose. Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-$HT_1$ agonists with and without a history of hypertension. Naratriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure and an 8% increase in mean aortic pressure was seen following dosing with 1.5 mg of subcutaneous naratriptan in a study evaluating 10 subjects with suspected CAD undergoing cardiac catheterization.

**Hypersensitivity:** Hypersensitivity (anaphylaxis/ anaphylactoid) reactions may occur in patients receiving naratriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

**PRECAUTIONS:**

**General:** Chest discomfort (including pain, pressure, heaviness, tightness) has been reported after administration of 5-$HT_1$ agonists, including AMERGE Tablets. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials with AMERGE Tablets. Because naratriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following naratriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of naratriptan, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following naratriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS).

nitrite-supplemented diet study were 7, 29, and 180 times, the exposure attained in humans given the maximum recommended daily dose of 5 mg. In both studies, there was an increase in the incidence of thyroid follicular hyperplasia in high-dose males and females and in thyroid follicular adenomas in high-dose males. In the standard diet study only, there was also an increase in the incidence of benign c-cell adenomas in the thyroid of high-dose males and females. The exposures achieved at the no-effect dose for thyroid tumors were 40 (standard diet) and 29 (nitrite-supplemented diet) times the exposure achieved in humans receiving the maximum recommended daily dose of 5 mg. In the nitrite-supplemented diet study only, the incidence of benign lymphocytic thymoma was increased in all treated groups of females. It was not determined if the nitrosated product is systemically absorbed. However, no changes were seen in the stomachs of rats in that study.

***Mutagenesis:*** Naratriptan was not mutagenic when tested in two gene mutation assays, the Ames test and the in vitro thymidine locus mouse lymphoma assay. It was not clastogenic in two cytogenetics assays, the in vitro human lymphocyte assay and the in vivo mouse micronucleus assay. Naratriptan can be nitrosated in vitro to form a mutagenic product (WHO nitrosation assay) that has been detected in the stomachs of rats fed a nitrite-supplemented diet.

***Impairment of Fertility:*** In a reproductive toxicity study in which male and female rats were dosed prior to and throughout the mating period with 10, 60, 170, or 340 mg/kg/day (plasma exposures [AUC] approximately 11, 70, 230, and 470 times, respectively, the human exposure at the maximum recommended daily dose [MRDD] of 5 mg), there was a treatment-related decrease in the number of females exhibiting normal estrous cycles at doses of 170 mg/kg/day or greater and an increase in preimplantation loss at 60 mg/kg/day or greater. In high-dose group males, testicular/epididymal atrophy accompanied by spermatozoa depletion reduced mating success and may have contributed to the observed preimplantation loss. The exposures achieved at the no-effect doses for preimplantation loss, anestrus, and testicular effects were approximately 11, 70, and 230 times, respectively, the exposures in humans receiving the MRDD.

In a study in which rats were dosed orally with 10, 60, or 340 mg/kg/day for 6 months, changes in the female reproductive tract including atrophic or cystic ovaries and anestrus were seen at the high dose. The exposure at the no-effect dose of 60 mg/kg was approximately 85 times the exposure in humans receiving the MRDD.

**Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women; therefore, naratriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

To monitor fetal outcomes of pregnant women exposed to AMERGE, Glaxo Wellcome Inc. maintains a Naratriptan Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 722-9292, ext. 39441.

In reproductive toxicity studies in rats and rabbits, oral administration of naratriptan was associated with developmental toxicity (embryolethality, fetal abnormalities, pup mortality, offspring growth retardation) at doses producing maternal plasma drug exposures as low as 11 and 2.5 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 5 mg.

When pregnant rats were administered naratriptan during the period of organogenesis at doses of 10, 60, or 340 mg/kg/day, there was a dose-related increase in embryonic death, with a statistically significant difference at the highest dose, and incidences of fetal structural variations (incomplete/irregular ossification of skull bones, sternebrae, ribs) were increased at all doses. The maternal plasma exposures (AUC) at these doses were approximately 11, 70, and 470 times the exposure in humans at the MRDD. The high dose was maternally toxic, as evidenced by decreased maternal body weight gain during gestation. A no-effect dose for developmental toxicity in rats exposed during organogenesis was not established.

When doses of 1, 5, or 30 mg/kg/day were given to pregnant Dutch rabbits throughout organogenesis, the incidence of a specific fetal skeletal malformation (fused sternebrae) was increased at the high dose, and increased incidences of embryonic death and fetal variations (major blood vessel variations, supernumerary ribs, incomplete skeletal ossification) were observed at all doses (4, 20, and 120 times, respectively, the MRDD on a body surface area basis). Maternal toxicity (decreased body weight gain) was evident at the high dose in this study. In a similar study in New Zealand White rabbits (1, 5, or 30 mg/kg/day throughout organogenesis), decreased fetal weights and increased incidences of fetal skeletal variations were observed at all doses (maternal exposures equivalent to 2.5, 19, and 140 times exposure in humans receiving the MRDD), while maternal body weight gain was reduced at 5 mg/kg or greater. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was not established.

When female rats were treated with 10, 60, or 340 mg/kg/day during late gestation and lactation, offspring behavioral impairment (tremors) and decreased offspring viability and growth were observed at doses of 60 mg/kg or greater, while maternal toxicity occurred only at the highest dose. Maternal exposures at the no-effect dose for developmental effects in this study were approximately 11 times the exposure in humans receiving the MRDD.

**Nursing Mothers:** Naratriptan-related material is excreted in the milk of rats. Therefore, caution should be exercised when considering the administration of AMERGE Tablets to a nursing woman.

**Pediatric Use:** Safety and effectiveness of AMERGE Tablets in pediatric patients (less than 18 years of age) have not been established.

One randomized, placebo-controlled clinical trial evaluating oral naratriptan (0.25 to 2.5 mg) in pediatric patients aged 12 to 17 years evaluated a total of 300 adolescent migraineurs. This study did not establish the efficacy of oral naratriptan compared to placebo in the treatment of migraine in adolescents (see CLINICAL TRIALS). Adverse events observed in this clinical trial were similar in nature to those reported in clinical trials in adults.

**Geriatric Use:** The use of naratriptan in elderly patients is not recommended.

AMERGE Tablets are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in elderly patients who have reduced renal function. In addition, elderly patients are more likely to have decreased hepatic function; they are at higher risk for CAD; and blood pressure increases may be more pronounced in the elderly. Clinical studies of AMERGE Tablets did not include patients over 65 years of age.

**ADVERSE REACTIONS: Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).**

**Incidence in Controlled Clinical Trials:** The most common adverse events were paresthesias, dizziness, drowsiness, malaise/fatigue, and throat/neck symptoms, which occurred at a rate of 2% and at least two times placebo rate. Since patients treated only one to three headaches in the controlled clinical trials, the opportunity for discontinuation of therapy in response to an adverse event was limited. In a long-term, open label study where patients were allowed to treat multiple migraine attacks for up to 1 year, 15 patients (3.6%) discontinued treatment due to adverse events.

Table 2 lists adverse events that occurred in five placebo-controlled clinical trials of approximately 1752 exposures to placebo and AMERGE Tablets in adult migraine patients. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use,

reporting behavior, and the kinds of patients treated may differ. Only events that occurred at a frequency of 2% or more in the AMERGE Tablets 2.5-mg treatment group and were more frequent in that group than in the placebo group are included in Table 2. From this table, it appears that many of these adverse events are dose related.

**Table 2: Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in Placebo-Controlled Migraine Trials**

| Adverse Event Type | Placebo (n = 498) | AMERGE 1 mg (n = 627) | AMERGE 2.5 mg (n = 627) |
|---|---|---|---|
| Atypical sensation | 1% | 2% | 4% |
| Paresthesias (all types) | <1% | 1% | 2% |
| Gastrointestinal | 5% | 6% | 7% |
| Nausea | 4% | 4% | 5% |
| Neurological | 3% | 4% | 7% |
| Dizziness | 1% | 1% | 2% |
| Drowsiness | <1% | 1% | 2% |
| Malaise/fatigue | 1% | 2% | 2% |
| Pain and pressure sensation | 2% | 2% | 4% |
| Throat/neck symptoms | 1% | 1% | 2% |

One event present in more than 1% of patients receiving AMERGE Tablets (vomiting) occurred more frequently on placebo than on naratriptan 2.5 mg.

AMERGE Tablets are generally well tolerated. Most adverse reactions were mild and transient.

The incidence of adverse events in placebo-controlled clinical trials was not affected by age or weight of the patients, duration of headache prior to treatment, presence of aura, use of prophylactic medications, or tobacco use. There was insufficient data to assess the impact of race on the incidence of adverse events.

**Other Events Observed in Association With the Administration of AMERGE Tablets:** In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of AMERGE Tablets in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc. limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n = 3557) exposed to oral naratriptan doses up to 10 mg. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those occurring in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1000 patients, and rare adverse events are those occurring in fewer than 1/1000 patients.

***Atypical Sensations:*** Frequent were warm/cold temperature sensations. Infrequent were feeling strange and burning/stinging sensation.

***Cardiovascular:*** Infrequent were palpitations, increased blood pressure, tachyarrhythmias, and abnormal ECG (PR prolongation, $QT_c$ prolongation, ST/T wave abnormalities, premature ventricular contractions, atrial flutter, or atrial fibrillation), and syncope. Rare were bradycardia, varicosities, hypotension, and heart murmurs.

***Ear, Nose, and Throat:*** Frequent were ear, nose, and throat infections. Infrequent were phonophobia, sinusitis, upper respiratory inflammation, and tinnitus. Rare were allergic rhinitis; labyrinthitis; ear, nose, and throat hemorrhage; and hearing difficulty.

***Endocrine and Metabolic:*** Infrequent were thirst and polydipsia, dehydration, and fluid retention. Rare were hyperlipidemia, hypercholesterolemia, hypothyroidism, hyperglycemia, glycosuria and ketonuria, and parathyroid neoplasm.

***Eye:*** Frequent was photophobia. Infrequent was blurred vision. Rare were eye pain and discomfort, sensation of eye pressure, eye hemorrhage, dry eyes, difficulty focusing, and scotoma.

***Gastrointestinal:*** Frequent were hyposalivation and vomiting. Infrequent were dyspeptic symptoms, diarrhea, gastrointestinal discomfort and pain, gastroenteritis, and constipation. Rare were abnormal liver function tests, abnormal bilirubin levels, hemorrhoids, gastritis, esophagitis, salivary gland inflammation, oral itching and irritation, regurgitation and reflux, and gastric ulcers.

***Hematological Disorders:*** Infrequent was increased white cells. Rare were thrombocytopenia, quantitative red cell or hemoglobin defects, anemia, and purpura.

***Lower Respiratory Tract:*** Infrequent were bronchitis, cough, and pneumonia. Rare were tracheitis, asthma, pleuritis, and airway constriction and obstruction.

***Musculoskeletal:*** Infrequent were muscle pain, arthralgia and articular rheumatism, muscle cramps and spasms, joint and muscle stiffness, tightness, and rigidity. Rare were bone and skeletal pain.

***Neurological:*** Frequent was vertigo. Infrequent were tremors, cognitive function disorders, sleep disorders, and disorders of equilibrium. Rare were compressed nerve syndromes, confusion, sedation, hyperesthesia, coordination disorders, paralysis of cranial nerves, decreased consciousness, dreams, altered sense of taste, neuralgia, neuritis, aphasia, hypoesthesia, motor retardation, muscle twitching and fasciculation, psychomotor restlessness, and convulsions.

***Non-Site Specific:*** Infrequent were chills and/or fever, descriptions of odor or taste, edema and swelling, allergies, and allergic reactions. Rare were spasms and mobility disorders.

***Pain and Pressure Sensations:*** Frequent were pressure/tightness/heaviness sensations.

***Psychiatry:*** Infrequent were anxiety, depressive disorders, and detachment. Rare were aggression and hostility, agitation, hallucinations, panic, and hyperactivity.

***Reproduction:*** Rare were lumps of female reproductive tract, breast inflammation, inflammation of vagina, inflammation of fallopian tube, breast discharge, endometrium disorders, decreased libido, and lumps of breast.

***Skin:*** Infrequent were sweating, skin rashes, pruritus, and urticaria. Rare were skin erythema, dermatitis and dermatosis, hair loss and alopecia, pruritic skin rashes, acne and folliculitis, allergic skin reactions, macular skin/rashes, skin photosensitivity, photodermatitis, skin flakiness, and dry skin.

***Urology:*** Infrequent were bladder inflammation and polyuria and diuresis. Rare were urinary tract hemorrhage, urinary urgency, pyelitis, and urinary incontinence.

**DRUG ABUSE AND DEPENDENCE:** In one clinical study enrolling 12 subjects, all of whom had experience using oral opiates and other psychoactive drugs, AMERGE Tablets produced less intense subjective responses ordinarily associated with many drugs of abuse than did codeine (30 to 90 mg).

**OVERDOSAGE:** A patient who was mildly hypertensive experienced a significant increase in blood pressure after administration of a 10-mg dose starting at 30 minutes (baseline value of 150/98 to 204/144 mmHg 225 minutes). This event resolved after treatment with antihypertensive therapy. Oral administration of 25 mg of naratriptan in one healthy young male subject increased blood pressure from 120/67 mmHg pretreatment up to 191/113 mmHg at approximately 6 hours postdose and resulted in adverse events including

medicine. You may need to read this leaflet again. This leaflet does not contain all the information on AMERGE Tablets. For further information or advice, ask your doctor or pharmacist.

**Information About Your Medicine:**

The name of your medicine is AMERGE (naratriptan hydrochloride) Tablets. It can be obtained only by prescription from your doctor. The decision to use AMERGE Tablets is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40), you should tell your doctor, who should evaluate you for heart disease in order to determine if AMERGE is appropriate for you. The majority of those who have taken AMERGE Tablets have not experienced any significant side effects. Rarely, deaths and/or serious heart problems have been reported with this class of medicines; in all but a few instances, however, these deaths and/or serious heart problems occurred in people with heart disease and it was not clear whether these medications were a contributing factor.

***1. The Purpose of Your Medicine:***

AMERGE Tablets are intended to relieve your migraine, but not to prevent or reduce the number of attacks you experience. Use AMERGE Tablets only to treat an actual migraine attack.

***2. Important Questions to Consider Before Taking AMERGE Tablets:***

If the answer to any of the following questions is **YES** or if you do not know the answer, then please discuss it with your doctor before you use AMERGE Tablets.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you not using adequate contraception? Are you breast-feeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Have you had a stroke, transient ischemic attacks or "TIAs", or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medication because of an allergy or other problems?
- Are you taking any other migraine medications, including other 5-$HT_1$ agonists such as IMITREX® (sumatriptan), or medications containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medication for depression such as selective serotonin reuptake inhibitors [SSRIs])?
- Have you had, or do you have, any disease of the kidney or liver?
- Is this headache different from your usual migraine attacks?

Remember, if you answered **YES** to any of the above questions, then discuss it with your doctor.

***3. The Use of AMERGE Tablets During Pregnancy:***

Do not use AMERGE Tablets if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

***4. How to Use AMERGE Tablets:***

For adults, the usual dose is a single tablet taken whole with fluids. It may be given at any time after the headache starts. For an individual attack, if you have no response to the first tablet, do not take a second tablet without first talking to your doctor. If you need more relief due to a partial response or return of your headache after the first tablet, a second tablet may be taken but not sooner than 4 hours following the first tablet. Do not take more than a total of two AMERGE Tablets in any 24-hour period. If you have kidney or liver disease, take as directed by your doctor.

***5. Side Effects to Watch for:***

lightheadedness, tension in the neck, tiredness, and loss of coordination. Blood pressure returned to near baseline by 8 hours after dosing without any pharmacological intervention.

Another subject experienced asymptomatic ischemic ECG changes likely due to coronary artery vasospasm approximately 2 hours following a 7.5-mg oral dose.

The elimination half-life of naratriptan is about 6 hours (see CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with AMERGE Tablets should continue for at least 24 hours or while symptoms or signs persist. There is no specific antidote to naratriptan. Standard supportive treatment should be applied as required. If the patient presents with chest pain or other symptoms consistent with angina pectoris, ECG monitoring should be performed for evidence of ischemia. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of naratriptan.

**DOSAGE AND ADMINISTRATION:** In controlled clinical trials, single doses of 1 and 2.5 mg of AMERGE Tablets taken with fluid were effective for the acute treatment of migraines in adults. A greater proportion of patients had headache response following a 2.5 mg dose than following a 1-mg dose (see CLINICAL TRIALS). Individuals may vary in response to doses of AMERGE Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 2.5-mg dose with the potential for a greater risk of adverse events. If the headache returns or if the patient has only partial response, the dose may be repeated once after 4 hours, for a maximum dose of 5 mg in a 24-hour period. There is evidence that doses of 5 mg do not provide a greater effect than 2.5 mg.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

**Renal Impairment:** The use of AMERGE is contraindicated in patients with severe renal impairment (creatinine clearance <15 mL/min) because of decreased clearance of the drug. (See CONTRAINDICATIONS and CLINICAL PHARMACOLOGY.) In patients with mild to moderate renal impairment, the maximum daily dose should not exceed 2.5 mg over a 24-hour period and a lower starting dose should be considered.

**Hepatic Impairment:** The use of AMERGE is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) because of decreased clearance (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY). In patients with mild or moderate hepatic impairment, the maximum daily dose should not exceed 2.5 mg over a 24-hour period and a lower starting dose should be considered (see CLINICAL PHARMACOLOGY).

**HOW SUPPLIED:** AMERGE Tablets 1 and 2.5 mg of naratriptan (base) as the hydrochloride. AMERGE Tablets, 1 mg, are white, D-shaped, film-coated tablets embossed with "GX CE3" on one side in blister packs of 9 tablets (NDC 0173-0561-00). AMERGE Tablets, 2.5 mg, are green, D-shaped, film-coated tablets embossed with "GX CE5" on one side in blister packs of 9 tablets (NDC 0173-0562-00).

**Store at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP).**

**PATIENT INFORMATION:** The following wording is contained in a separate leaflet provided for patients.

**Information for the Patient**
**AMERGE™ (naratriptan hydrochloride) Tablets**

Please read this leaflet carefully before you take AMERGE Tablets. This leaflet provides a summary of the information available about your medicine. Please do not throw away this leaflet until you have finished your

- Some patients experience pain or tightness in the chest or throat when using AMERGE Tablets. If this happens to you, then discuss it with your doctor before using any more AMERGE Tablets. If the chest pain, tightness, or pressure is severe or does not go away, call your doctor immediately.
- If you have sudden and/or severe abdominal pain following AMERGE Tablets, call your doctor immediately.
- Shortness of breath; wheeziness; heart throbbing, swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor immediately. Do not take any more AMERGE Tablets unless your doctor tells you to do so.
- Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with AMERGE Tablets. A few people may feel drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.
- If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

***6. What to Do if an Overdose is Taken:***

If you have taken more medication than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately.

***7. Storing Your Medicine:***

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Store your medication away from heat and light. Do not store at temperatures above 77°F (25°C). If your medication has expired (the expiration date is printed on the treatment pack), throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

**GlaxoWellcome**
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
Made in England

US Patent No. 4,997,841



February 1998 RL-534

# EXHIBIT 5

U.S. Patent 4,997,841

# United States Patent [19]

**Oxford et al.**

[11] **Patent Number: 4,997,841**

[45] **Date of Patent: Mar. 5, 1991**


[54] **INDOLE DERIVATIVES**


[75] Inventors: **Alexander W. Oxford**, Royston; **Darko Butina**, Arlesey; **Martin R. Owen**, Puckeridge, all of United Kingdom

[73] Assignee: **Glaxo Group Limited**, England



[21] Appl. No.: **231,274**

[22] Filed: **Aug. 12, 1988**

[30] **Foreign Application Priority Data**

| | | | |
|---|---|---|---|
| Aug. 13, 1987 | [GB] | United Kingdom | 8719167 |
| Jun. 14, 1988 | [GB] | United Kingdom | 8814002 |
| Jun. 17, 1988 | [GB] | United Kingdom | 8814481 |

[51] **Int. Cl.**[5] ..... **A61K 31/445**; C07D 401/04

[52] **U.S. Cl.** ..... **514/323**; 514/339; 546/201; 546/273

[58] **Field of Search** ..... 546/201; 514/323



[56] **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
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| 4,548,939 | 10/1985 | Kennis et al. | 514/265 |
| 4,711,893 | 12/1987 | Hausberg et al. | 514/339 |

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| | | |
|---|---|---|
| 0147107 | 7/1985 | European Pat. Off. . |
| 0200322 | 11/1986 | European Pat. Off. . |
| 1556919 | 11/1979 | United Kingdom . |
| 2124210A | 2/1984 | United Kingdom . |
| 2150932A | 7/1985 | United Kingdom . |
| 2162522A | 2/1986 | United Kingdom . |
| 2168973A | 7/1986 | United Kingdom . |

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Peroutka et al., *J. Pharm. Exp. Ther.*, 237 (3), 901–906 (1986).

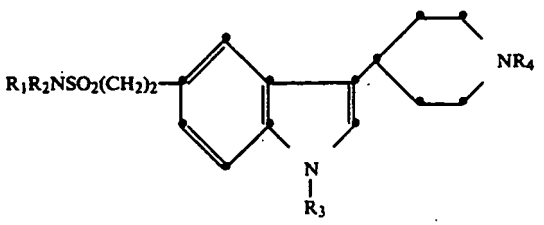
Taylor et al., *J. Pharm. Exp. Ther.*, 236 (1), 118–125 (1986).


*Primary Examiner*—Jane T. Fan

*Attorney, Agent, or Firm*—Bacon & Thomas


[57] **ABSTRACT**

Compounds are disclosed of formula (I)




(I)

wherein

$R_1$ represents H or $C_{1-6}$ alkyl;

$R_2$ represents H or $C_{1-6}$ alkyl;

$R_3$ represents H;

$R_4$ represents H or $C_{1-3}$ alkyl; and pharmaceutically acceptable salts and solvates (for example hydrates thereof.

The compounds are indicated as useful for the treatment of migraine, cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders.

Processes and intermediates for their preparation and pharmaceutical compositions containing them are also disclosed.


**18 Claims, No Drawings**

# INDOLE DERIVATIVES

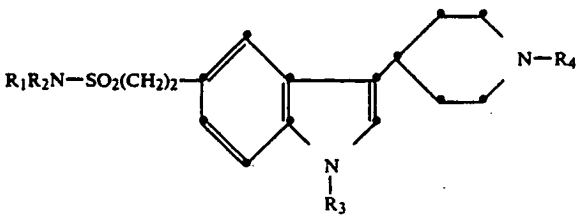
This invention relates to in dole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use, in particular to compounds and compositions of use in the treatment of migraine.

It has been suggested that the pain of migraine may be associated with excessive dilation of the cranial vasculature and known treatments for migraine include the administration of compounds having vasoconstrictor properties such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and potentially dangerous side effects. Migraine may also be treated by administering an analgesic usually in combination with an antiemetic but such treatments are of limited value.

More recently, indole derivatives which are selective $5HT_1$-like receptor agonists and which exhibit selective vasoconstrictor activity have been described in the art as useful in the treatment of migraine (see for example A. Doenicke, J. Brand, V. L. Perrin, *Lancet*, 1988, 1309–1311).

We have now found a novel group of indole derivatives which not only exhibit $5HT_1$-like receptor agonist activity and selective vasoconstriction but also unexpectedly have an enhanced overall bioavailability index following administration, in particular following non-parenteral administration.

Thus the invention provides in a first aspect an indole of formula (I).




wherein

$R_1$ represents a hydrogen atom or a $C_{1-6}$ alkyl group;

$R_2$ represents a hydrogen atom or a $C_{1-6}$ alkyl group;

$R_3$ represents a hydrogen atom, $R_4$ represents a hydrogen atom or a $C_{1-3}$ alkyl group and pharmaceutically acceptable salts and solvates (for example hydrates) therof.

All optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof are embraced by the invention.

As used herein, an alkyl group may be a straight chain (such as a methyl or ethyl) or branched chain alkyl group.

Suitable pharmaceutically acceptable salts of the indoles of general formula (I) include acid addition salts formed with organic or inorganic acids, for example, hydrochlorides, hydrobromimdes, sulphates, fumarates and maleates. Other salts may be useful in the preparation of compounds of formula (I), e.g. creatinine sulphate adducts.

A preferred class of compounds represented by the general formula (I) is that wherein $R_1$ represents a hydrogen atom or a $C_{1-3}$ alkyl group such as a methyl group.

Another preferred class of compounds is that wherein $R_2$ represents a hydrogen atom or a $C_{1-3}$ alkyl group such as methyl.

Conveniently, $R_1$ and $R_2$ together comprise from 1 to 3 carbon atoms.

The substituent $R_4$ is conveniently a $C_{1-3}$ alkyl group such as methyl.

Preferred compounds according to the invention include:

N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide;

N,N-Dimethyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide;

N-Ethyl-3-(4-piperidinyl)-1H-indole-5-ethanesulphonamide;

N-Methyl-3-(4-piperidinyl)-1H-indole-5-ethanesulphonamide;

3(1-Methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide;

and pharmaceutically acceptable salts and solvates thereof.

The selective $5HT_1$-like receptor agonist activity and selective vasoconstrictor activity of the compounds of the invention have been demonstrated in vitro. In addition, compounds of the invention selectively constrict the carotid arterial bed of the anaesthetised dog whilst having negligible effect on blood pressure.

Following non-parenteral, including intra-duodenal administration, the compounds of the invention show an enhanced bioavailability index in animals.

Compounds of the invention are useful in treating conditions associated with cephalic pain. In particular the compounds are useful in the treatment of migraine, cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders and in alleviating the symptoms associated therewith.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate (e.g. hydrate) thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

In a further aspect there is provided a compound of formula (I) or a salt or solvate thereof for use in therapy, in particular in human medicine. It will be appreciated that use in therapy embraces but is not necessarily limited to use of a compound of formula (I) or a salt or solvate thereof as an active therapeutic substance.

There is also provided as a further aspect of the invention the use of a compound of formula (I) in the preparation of a medicament for use in the treatment of conditions associated with cephalic pain in particular migraine, cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders.

In an alternative or further aspect there is provided a method for the treatment of mammal, including man, comprising administration of an effective amount of a compound of formula (I) or salt or solvate thereof in particular in the treatment of conditions associated with cephalic pain and in alleviating the symptoms associated therewith.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds according to

# EXHIBIT 6

Terminal Disclaimer for
U.S. Patent 4,997,841

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

OXFORD et al.

Serial No.:07/231,274 Group Art Unit: 121

Filed: August 12, 1988 Examiner: FAN

For: INDOLE DERIVATIVES

TERMINAL DISCLAIMER

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Your petitioner, GLAXO GROUP LIMITED, represents that it is the owner by assignment recorded at Reel 4938, Frames 647-648 of the entire right and title to the above-identified patent application.

Your petitioner hereby disclaims the terminal part of any patent granted on the above-identified application which would extend beyond the expiration date of the full statutory term of any patent issuing from application Serial No. 07/231,260 filed August 12, 1988, the entire right and title to which is assigned to petitioner by assignment recorded at Reel 4930 Frames 640-641; and hereby agrees that any patent so granted on the above-identified application, 07/231,274, shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to any patent issuing from application Serial No. 07/231,260, this agreement to run with any patent granted on the above-identified application and to be binding upon the grantee, its successors or assigns.

Petitioner does not disclaim any terminal part of any patent granted on the above-identified application prior to

the expiration date of the full statutory term of any patent issuing from application Serial No.07/231,260 in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, if found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321(a), has all claims cancelled by a reexamination certificate, or is otherwise terminated prior to the expiration of its statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

Signature

BARRY ANTHONY NEWSAM

Typed Name

ATTORNEY

Title (authorized representative for binding petitioner)

1st August 1990

Date

WP/QX231,274.DIS

# EXHIBIT 7

Patent Term Extension Calculations

# EXHIBIT 7

## Patent Term Extension Calculations

**Patent Issue Date:** **3/5/91**

**IND Effective Date:** **7/5/95**

7/05/95 - 12/31/95 = 180
1/01/96 - 12/03/96 = 338
518 x 0.5 = 259 days

**NDA Submission Date:** **12/04/96**

12/04/96 - 12/31/96 = 28
1/01/97 - 12/31/97 = 365
1/01/98 - 2/10/98 = 41
434 x 1 = 434 days

**NDA Approval Date:** **2/10/98**

**Total Patent Term Extension:** 693 days

## Patent Term Extension + Expiration 20 years from Filing

**20 yr Expiration** **8/12/08**

8/12/08 - 12/31/08 = 142
1/01/09 - 12/31/09 = 365
1/01/10 - 7/5/10 = 186
693 days

**20 yr Expiration**
**+ 693 day Patent Term Extension:** **7/5/10**

## 14 yr Cap from NDA Approval Date

**NDA Approval Date:** **2/10/98**

2/10/98 + 14 yrs = 2/10/12

**14 year Patent Term Cap Date:** ***2/10/12***

# EXHIBIT 8

Document Chronology / Due Diligence Log

for

IND 48,120

# Chronology for IND 48, 120
# Naratriptan Tablets

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 05-Jun-95 | Glaxo Wellcome Correspondence | Initial Investigational New Drug Application | | 000 |

IND for Naratriptan Tablets
Initial Investigational New Drug Application
IND to be Filed with the Division of Neuropharmacological Drug Products

Serial No.:

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| | | | | |
|---|---|---|---|---|
| 05-Jul-95 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol | | 001 |

IND 48,120; Naratriptan (GR85548) Tablets
Protocol Amendment: New Protocol
Serial No.: 001

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| | | | | |
|---|---|---|---|---|
| 05-Jul-95 | Food and Drug Administration Telephone Conversation | General Teleconference | | |

IND 48,120; Naratriptan (GR85548) Tablets
Status Update

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 31-Jul-95 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add | 002 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 002 | | |
| 28-Aug-95 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol<br>Protocol Amendment: New Investigator<br>Protocol Amendment: Change in Protocol<br>General Correspondence | Investigator Add | 003 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Protocol<br>Protocol Amendment: New Investigator<br>Protocol Amendment: Change in Protocol<br>General Correspondence: Change in Medical Monitor<br>Serial No.: 003 | | |
| 13-Sep-95 | Food and Drug Administration Correspondence | Comment/Information Request | Clinical<br>CMC<br>Nonclinical | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment: Clinical<br>FDA Comment: CMC<br>FDA Comment: Nonclinical | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 08-Nov-95 | Glaxo Wellcome Correspondence | Protocol Amendment: Change in Protocol<br>Protocol Amendment: New Investigator | Clinical<br>Investigator Add | 007 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: Change in Protocol<br>Protocol Amendment: New Investigator<br>Serial No.: 007 | | |
| 08-Nov-95 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Request | | |
| 20-Nov-95 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |
| | | NDA 20-080; Imitrex® (sumatriptan succinate) Injection<br>Response to FDA Request/Comment | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 28-Sep-95 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | | 004 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 004 | | |
| 19-Oct-95 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol<br>Protocol Amendment: Change in Protocol<br>Information Amendment: Chemistry Manufacturing and Controls | | 005 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Protocol<br>Protocol Amendment: Change in Protocol<br>Information Amendment: Chemistry Manufacturing and Controls<br>Serial No.: 005 | | |
| 07-Nov-95 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | Clinical | 006 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Response to FDA Request/Comment<br>Serial No.: 006 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 19-Jan-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol<br>Protocol Amendment: New Investigator | | 010 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Protocol<br>Protocol Amendment: New Investigator<br>Serial No.: 010 | | |
| 19-Jan-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | BA/BE | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |
| 24-Jan-96 | Glaxo Wellcome Correspondence | Information Amendment: Nonclinical<br>Amendment: Other | | 011 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Information Amendment: Nonclinical: Toxicology<br>Amendment: IND Safety Report<br>Serial No.: 011 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 05-Dec-95 | Food and Drug Administration Correspondence | Comment/Information Request | Clinical | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment | | |
| 15-Dec-95 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Sub-investigator Add | 008 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 008 | | |
| 04-Jan-96 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>IND 45,147; 311C90 Tablets<br>FDA Comment: General Principles | | |
| 15-Jan-96 | Glaxo Wellcome Correspondence | Protocol Amendment: Change in Protocol | Clinical | 009 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: Change in Protocol<br>Serial No.: 009 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 07-Feb-96 | Glaxo Wellcome Correspondence | General Correspondence | Meeting Request | 012 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Correspondence<br>Request for Pre-NDA Meeting<br>Serial No.: 12 | | |
| 15-Feb-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |
| 19-Feb-96 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | CMC | 014 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Response to FDA Request/Comment<br>Serial No.: 014 | | |
| 19-Feb-96 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Response to FDA Request/Comment | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 20-Feb-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |
| 23-Feb-96 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | 015 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Response to FDA Request/Comment<br>Serial No.: 015 | | |
| 29-Feb-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add | 016 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 016 | | |
| 05-Mar-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | BA/BE | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 06-Mar-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |
| 07-Mar-96 | Food and Drug Administration Correspondence | Comment/Information Request | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment | | |
| 14-Mar-96 | Glaxo Wellcome Correspondence | Amendment: Other | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Amendment: Other<br>Serial No.: | | |
| 15-Mar-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | Other | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 18-Mar-96 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | 017 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Response to FDA Request/Comment<br>Serial No.: 017 | | |
| 25-Mar-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | BA/BE | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |
| 25-Mar-96 | Glaxo Wellcome Correspondence | Protocol Amendment: Change in Protocol | | 019 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: Change in Protocol<br>Serial No.: 019 | | |
| 02-Apr-96 | Glaxo Wellcome Correspondence | General Correspondence | | 020 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Correspondence: Minutes of pre-NDA Meeting<br>Serial No.: 020 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 11-Apr-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol<br>Protocol Amendment: New Investigator | | 021 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Protocol<br>Protocol Amendment: New Investigator<br>Serial No.: 021 | | |
| 12-Apr-96 | Glaxo Wellcome Correspondence | Information Amendment: Clinical | | 022 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Information Amendment: Clinical<br>Serial No.: 022 | | |
| 16-Apr-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | | 023 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 023 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 14-May-96 | Food and Drug Administration Correspondence | Comment/Information Request | CMC | |

IND 48,120; Naratriptan (GR85548) Tablets
NDA 20-626; Imitrex® (sumatriptan) Nasal Spray 5mg, 10mg and 20mg
Information Request: CMC

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|---|---|---|---|---|
| 21-May-96 | Glaxo Wellcome Correspondence | Information Amendment: Nonclinical | | 024 |

IND 48,120; Naratriptan (GR85548) Tablets
Information Amendment: Nonclinical
Serial No.: 024

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|---|---|---|---|---|
| 23-May-96 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | 025 |

IND 48,120; Naratriptan (GR85548) Tablets
Response to FDA Request/Comment
Serial No.: 025

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 24-May-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | | 026 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 026 | | |
| 17-Jun-96 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | CMC | 027 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Response to FDA Request/Comment: CMC<br>Serial No.: 027 | | |
| 17-Jun-96 | Food and Drug Administration Telephone Conversation | Comment/Information Request | CMC | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Information Request: CMC | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 20-Jun-96 | Glaxo Wellcome Correspondence | Information Amendment: Chemistry Manufacturing and Controls | | 028 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Information Amendment: Chemistry Manufacturing and Controls<br>Request for Pre-NDA Meeting<br>Serial No.: 028 | | |
| 24-Jun-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | | 029 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 029 | | |
| 01-Jul-96 | Food and Drug Administration Telephone Conversation | Comment/Information Request | CMC | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment: CMC | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 08-Jul-96 | Glaxo Wellcome Correspondence | General Correspondence | | 030 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Correspondence: Request for Review of Seromax as a Proprietary Name<br>Serial No.: 030 | | |
| 01-Aug-96 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | 031 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Response to FDA Request/Comment<br>Serial No.: 031 | | |
| 07-Aug-96 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Clinical | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment: Clinical | | |
| 08-Aug-96 | Food and Drug Administration Correspondence | Comment/Information Request | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 19-Aug-96 | Food and Drug Administration Telephone Conversation | Comment/Information Request | CMC | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment: CMC<br>Comments Regarding Draft Minutes of CMC Pre-NDA Meeting | | |
| 22-Aug-96 | Glaxo Wellcome Correspondence | Annual Report | | 032 |
| | | | CMC | |
| | | IND 48,120; Naratriptan Tablets<br>Annual Report<br>Serial No.: 032 | | |
| 23-Aug-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator<br>Protocol Amendment: Change in Protocol | | 033 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Protocol Amendment: Change in Protocol<br>Serial No.: 033 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 26-Aug-96 | Glaxo Wellcome Correspondence | Information Amendment: Chemistry Manufacturing and Controls | | 035 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Information Amendment: Chemistry Manufacturing and Controls<br>Serial No.: 035<br>Minutes of CMC Pre-NDA Meeting | | |
| 26-Aug-96 | Glaxo Wellcome Correspondence | General Correspondence | | 034 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Correspondence<br>Serial No.: 034 | | |
| 26-Aug-96 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>RECORD OF FAX<br>General Correspondence:<br>Naratriptan Tablets - Electronic Files for FDA<br>Request for Waiver of Paper Copies | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 08-Sep-96 | Glaxo Wellcome Correspondence | General Correspondence | Other | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Correspondence | | |
| 10-Sep-96 | Glaxo Wellcome Correspondence | Information Amendment: Clinical | | 036 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Information Amendment: Clinical: Final Study Report<br>Serial No.: 036 | | |
| 12-Sep-96 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment | | |
| 18-Sep-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 19-Sep-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol | | 037 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Protocol<br>Serial No.: 037 | | |
| 19-Sep-96 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>FDA Comment: Response from Nomenclature Committee | | |
| 01-Oct-96 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | | 038 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 038 | | |
| 02-Oct-96 | Glaxo Wellcome Correspondence | Information Amendment: Clinical | | 039 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Information Amendment: Clinical: Final Study Report<br>Serial No.: 039 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 04-Oct-96 | Glaxo Wellcome Correspondence | General Correspondence | CMC | 040 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Correspondence: Request for Review of Naramig as Proprietary Name<br>Serial No.: 040 | | |
| 07-Oct-96 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Information Request | | |
| 16-Oct-96 | Glaxo Wellcome Telephone Conversation | General Teleconference | CMC | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Record of Telecon: CMC | | |
| 24-Oct-96 | Glaxo Wellcome Correspondence | General Correspondence | | 041 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Correspondence<br>Serial No.: 041 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 25-Nov-96 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Correspondence<br>Proposal to Provide Electronic Electronic Files | | |
| 14-Jan-97 | Food and Drug Administration Correspondence | Acknowledgement | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Approval of Waiver of Requirement to Provide CRF Tabulations | | |
| 07-Feb-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | | 046 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 046 | | |
| 26-Jun-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>General Teleconference<br>Update on status of CMC Review | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 30-Jun-97 | Glaxo Wellcome Correspondence | Annual Report | CMC | 047 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Annual Report<br>Serial No.: 047 | | |
| 21-Aug-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol | | 048 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Serial No.: 048<br>IND 32,299; GR43175C (sumatriptan succinate) Tablets<br>Serial No.: 307<br>Protocol Amendment: New Protocol | | |
| 08-Sep-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol<br>Information Amendment: Chemistry Manufacturing and Controls | | 049 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Protocol<br>Information Amendment: Chemistry Manufacturing and Controls<br>Serial No.: 049 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 24-Sep-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | | 050 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Serial No.: 050<br>IND 32,299; GR43175C (sumatriptan succinate) Tablets<br>Serial No.: 311<br>Protocol Amendment: New Investigator | | |
| 30-Sep-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Protocol<br>Protocol Amendment: New Investigator | | 051 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Serial No.: 051<br>Protocol Amendment: New Protocol<br>Protocol Amendment: New Investigator | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 28-Oct-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add | 052 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 052 | | |
| 28-Oct-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add | 053 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Serial No.: 053<br>IND 32,299; GR43175C (sumatriptan succinate) Tablets<br>Serial No.: 313<br>Protocol Amendment: New Investigator | | |
| 18-Nov-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add | 054 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Serial No.: 054<br>IND 32,299; GR43175C (sumatriptan succinate) Tablets<br>Serial No.: 315<br>Protocol Amendment: New Investigator | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 24-Nov-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add<br>Other 1572 Change | 055 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 055 | | |
| 15-Dec-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add<br>Other 1572 Change | 056 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 056 | | |
| 22-Dec-97 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add<br>Other 1572 Change | 057 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Serial No.: 057<br>IND 32,299; GR43175C (sumatriptan succinate) Tablets<br>Serial No.: 318<br>Protocol Amendment: New Investigator | | |
| 16-Jan-98 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add<br>Other 1572 Change | 058 |
| | | IND 48,120; Naratriptan (GR85548) Tablets<br>Protocol Amendment: New Investigator<br>Serial No.: 058 | | |

Application: IND 48120; Naratriptan (GR85548) Tablets

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 03-Feb-98 | Glaxo Wellcome Correspondence | Information Amendment: Chemistry Manufacturing and Controls | CMC | 059 |

IND 48,120; Naratriptan (GR85548) Tablets
Information Amendment: Chemistry Manufacturing and Controls, CMC
Serial No.: 059

# EXHIBIT 9

Document Chronology / Due Diligence Log

for

NDA 20-763

# Chronology for NDA 20-763
# AMERGE™ (naratriptan chloride) Tablets

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 04-Dec-96 | Glaxo Wellcome Correspondence | Original Submission | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Original New Drug Application | | |
| 04-Dec-96 | Glaxo Wellcome Correspondence | General Correspondence | CMC Field Copy | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Original Application<br>FIELD COPY SUBMISSION | | |
| 04-Dec-96 | Glaxo Wellcome Correspondence | User Fee | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Initial Application User Fee | | |
| 04-Dec-96 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request: Clinical | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 13-Dec-96 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |
| 16-Dec-96 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request | | |
| 06-Jan-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |
| 06-Jan-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 20-Jan-97 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Correspondence | | |
| 23-Jan-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 30-Jan-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |
| 31-Jan-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |
| 06-Feb-97 | Food and Drug Administration<br>Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Status Update | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 14-Jan-97 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Correspondence | | |
| 16-Jan-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |
| 17-Jan-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |
| 17-Jan-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | Labeling | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>NDA 20-132; Imitrex® (sumatriptan succinate) Tablets<br>FDA Comment: Labeling | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 12-Feb-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | Nonclinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 19-Feb-97 | Glaxo Wellcome Correspondence | General Correspondence | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Correspondence<br>Clinical Investigations Data to Support Clinical Inspections | | |
| 19-Feb-97 | Food and Drug Administration Correspondence | Acknowledgement | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Acknowledgement: Notice of NDA Filing | | |
| 24-Feb-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Statistical<br>Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request: Statistics<br>Information Request: Clinical | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 06-Feb-97 | Food and Drug Administration Correspondence | Comment/Information Request | Nonclinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg FDA Comment | | |
| 07-Feb-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | BA/BE | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request/Comment | | |
| 07-Feb-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Nonclinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |
| 10-Feb-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 10-Mar-97 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Correspondence: Clinical Investigations Data to Support Clinical Inspections | | |
| 10-Mar-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>FDA Comment: CMC | | |
| 10-Mar-97 | Food and Drug Administration Correspondence | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 24-Feb-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |
| 26-Feb-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request/Comment | | |
| 27-Feb-97 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg General Correspondence Clinical Investigations Data to Support Clinical Inspection | | |
| 03-Mar-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 11-Mar-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Record of Telecon | | |
| 13-Mar-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Record of Telecon | | |
| 17-Mar-97 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Correspondence | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 01-Apr-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request: CMC | | |
| 02-Apr-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request/Comment | | |
| 08-Apr-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Record of Telecon | | |
| 09-Apr-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request/Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 09-Apr-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 10-Apr-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment: Clinical | | |
| 11-Apr-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 14-Apr-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 15-Apr-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 17-Apr-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>FDA Comment | | |
| 17-Apr-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |
| 17-Apr-97 | Food and Drug Administration<br>Correspondence | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 22-Apr-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |
| 23-Apr-97 | Food and Drug Administration<br>Correspondence | User Fee Invoice | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>User Fee Reconciliation Request: Notice of refund | | |
| 01-May-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 01-May-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment: CMC<br>Environmental Assessment | | |
| 01-May-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Record of Telecon | | |
| 01-May-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 08-May-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Statistical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 16-May-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |
| 19-May-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Record of Telecon | | |
| 22-May-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Record of Telecon | | |
| 27-May-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request/Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 08-May-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 14-May-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Nonclinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |
| 14-May-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Record of Telecon | | |
| 15-May-97 | Glaxo Wellcome Correspondence | 120-Day Safety Update | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Four Month Safety Update | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 27-May-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 03-Jun-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 04-Jun-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>FDA Comment | | |
| 06-Jun-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Record of Telecon | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 06-Jun-97 | Glaxo Wellcome Correspondence | Amendment to Pending Application | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Amendment to Pending Application: CMC Stability Update | | |
| 10-Jun-97 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Correspondence: Request for Review of Proprietary Name | | |
| 10-Jun-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Record of Telecon | | |
| 13-Jun-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 24-Jun-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 25-Jun-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |
| 26-Jun-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>FDA Comment | | |
| 26-Jun-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 27-Jun-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |
| 27-Jun-97 | Food and Drug Administration Correspondence | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Information Request | | |
| 30-Jun-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request/Comment | | |
| 01-Jul-97 | Glaxo Wellcome Correspondence | General Correspondence | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg General Correspondence: Corrected table for Study S2WB3004 | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 01-Jul-97 | Glaxo Wellcome Correspondence | Amendment to Pending Application | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Amendment to Pending Application: CMC<br>FIELD COPY SUBMISSION | | |
| 03-Jul-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 08-Jul-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>NDA 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets<br>FDA Comment | | |
| 08-Jul-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 09-Jul-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 09-Jul-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 10-Jul-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 10-Jul-97 | Food and Drug Administration Correspondence | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>FDA Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 13-Jul-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference: CMC | | |
| 14-Jul-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Record of Telecon | | |
| 14-Jul-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Record of Telecon | | |
| 22-Jul-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 22-Jul-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Comment/Information Request | | |
| 25-Jul-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request/Comment | | |
| 25-Jul-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg General Teleconference | | |
| 29-Jul-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Response to FDA Request/Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 31-Jul-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference | | |
| 01-Aug-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 01-Aug-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment: CMC<br>Request to submit unofficial copy of response to CMC Questions | | |
| 01-Aug-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 01-Aug-97 | Food and Drug Administration Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference | | |
| 04-Aug-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment: CMC<br>Unofficial FAX Copy of Responses to CMC Questions of July 9, 1997 | | |
| 05-Aug-97 | Glaxo Wellcome Correspondence | Amendment to Pending Application | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Amendment to Pending Application: Response to Inquiry | | |
| 05-Aug-97 | Glaxo Wellcome FAX/E-mail | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 11-Aug-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment: CMC | | |
| 20-Aug-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment and Stability Update: CMC | | |
| 20-Aug-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment and Stability Update: CMC<br>FIELD COPY SUBMISSION | | |
| 20-Aug-97 | Food and Drug Administration Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 06-Aug-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 07-Aug-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 07-Aug-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request: CMC<br>Comments regarding telefacsimile of August 4, 1997 | | |
| 11-Aug-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 03-Sep-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference: CMC<br>Environmental Assessment FONSI Status | | |
| 04-Sep-97 | Glaxo Wellcome Correspondence | General Correspondence | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Correspondence: CMC<br>Submission of Electronic Copy | | |
| 04-Sep-97 | Glaxo Wellcome Correspondence | General Correspondence | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Correspondence: CMC<br>FIELD COPY SUBMISSION | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 21-Aug-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference | | |
| 29-Aug-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 02-Sep-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 03-Sep-97 | Food and Drug Administration FAX/E-mail | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 11-Sep-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment | | |
| 07-Oct-97 | Glaxo Wellcome Correspondence | Amendment to Pending Application | Labeling | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Amendment to Pending Application: Labeling | | |
| 07-Oct-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | Labeling | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference: Labeling | | |
| 08-Oct-97 | Glaxo Wellcome FAX/E-mail | Response to FDA Request/Comment | Labeling | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment: Labeling | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 08-Sep-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Comment/Information Request | | |
| 08-Sep-97 | Food and Drug Administration Telephone Conversation | General Teleconference | Advisory Committee Meeting | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg General Teleconference: CMC | | |
| 08-Sep-97 | Food and Drug Administration Correspondence | Comment/Information Request | | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Comment/Information Request for Sample of Materials for Methods Validation | | |
| 09-Sep-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Labeling | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg Comment/Information Request: Labeling | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 10-Oct-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Labeling | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request: Labeling | | |
| Comment: clinical disability claims | | | | |
| 17-Oct-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Response to FDA Request/Comment: CMC | | |
| 22-Oct-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 23-Oct-97 | Glaxo Wellcome FAX/E-mail | General Memorandum | Clinical<br>Labeling<br>Other | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Memorandum: Comment/Information Reqeust | | |
| 24-Oct-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request: Clinical | | |
| 26-Oct-97 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | CMC | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Comment/Information Request: CMC | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 27-Oct-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | Clinical Safety | |

NDA 20-763; Naratriptan Tablets 2.5mg
Response to FDA Request/Comment

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 29-Oct-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | Clinical | |

NDA 20-763; Naratriptan Tablets 2.5mg
Response to FDA Request/Comment: Clinical

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 03-Nov-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference: Clinical | | |
| 04-Nov-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | Request Status Update | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>General Teleconference | | |
| 05-Nov-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 14-Nov-97 | Food and Drug Administration FAX/E-mail | Comment/Information Request | Labeling | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request: Labeling | | |
| 17-Nov-97 | Food and Drug Administration FAX/E-mail | Comment/Information Request | Clinical | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Comment/Information Request: Dissolution Method and Specifications | | |
| 21-Nov-97 | Glaxo Wellcome Correspondence | General Correspondence | Advertising/Promotion<br>Labeling | |
| | | NDA 20-763; Naratriptan Tablets 2.5mg<br>Request for Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 21-Nov-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment<br>Amendment to Pending Application | Labeling<br>Labeling | |
| | | NDA 20-763; AMERGE (naratriptan hydrochloride) Tablets 1 and 2.5mg<br>Amendment to Pending Application<br>Response to Agency Comments<br>Revised Labeling | | |
| 21-Nov-97 | Glaxo Wellcome Telephone Conversation | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment | | |
| 24-Nov-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | Clinical | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment: Clinical | | |
| 26-Nov-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | BA/BE | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 26-Nov-97 | Glaxo Wellcome FAX/E-mail | Response to FDA Request/Comment | BA/BE<br>CMC | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment: CMC | | |
| 01-Dec-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | CMC | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment<br>Provision of Replacement Methods Validation Samples | | |
| 01-Dec-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment<br>General Correspondence | CMC<br>CMC Field Copy | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment: CMC<br>FIELD COPY SUBMISSION | | |
| 01-Dec-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | Clinical | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment: Clinical | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 04-Dec-97 | Food and Drug Administration Correspondence | Acknowledgement | 090-Day Review Extension | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Acknowledgement: 090-Day Review Extension | | |
| 04-Dec-97 | Food and Drug Administration Correspondence | General Correspondence | Other | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Correspondence: Other: Approval of Proposed Logo for Amerge for Promotional Pieces | | |
| 10-Dec-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | Clinical | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Teleconference | | |
| 15-Dec-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | Labeling | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment<br>Final Printed Labeling | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 15-Dec-97 | Food and Drug Administration FAX/E-mail | General Memorandum | Status Update | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg Comment/Information Request: Dissolution Specification | | |
| 16-Dec-97 | Glaxo Wellcome Telephone Conversation | General Teleconference | BA/BE | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg General Teleconference: CMC, BA/BE | | |
| 17-Dec-97 | Glaxo Wellcome Correspondence | Response to FDA Request/Comment | Clinical | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg Response to FDA Request/Comment | | |
| 17-Dec-97 | Food and Drug Administration Telephone Conversation | Comment/Information Request | Clinical Safety | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg General Teleconference | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 13-Jan-98 | Food and Drug Administration<br>Telephone Conversation | Comment/Information Request | Labeling | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Comment/Information Request: Labeling | | |
| 13-Jan-98 | Food and Drug Administration<br>FAX/E-mail | Comment/Information Request | CMC | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Comment/Information Request: Dissolution Specification | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 23-Dec-97 | Glaxo Wellcome FAX/E-mail | General Memorandum | Other | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Memorandum: Other: Contact numbers while company closed for Christmas Holidays | | |
| 23-Dec-97 | Glaxo Wellcome FAX/E-mail | General Memorandum | Other | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Memorandum: Other | | |
| 09-Jan-98 | Food and Drug Administration FAX/E-mail | Comment/Information Request | Labeling | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Comment/Information Request: Labeling | | |
| 13-Jan-98 | Glaxo Wellcome FAX/E-mail | General Memorandum | Labeling | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Memorandum: Labeling | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 15-Jan-98 | Glaxo Wellcome Correspondence | Amendment to Pending Application | Labeling | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Amendment to Pending Application: Labeling | | |
| 15-Jan-98 | Food and Drug Administration FAX/E-mail | Comment/Information Request | CMC | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Comment/Information Request: Dissolution Specifications | | |
| 16-Jan-98 | Glaxo Wellcome Correspondence | General Correspondence | CMC | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Correspondence: Dissolution Specifications | | |
| 16-Jan-98 | Glaxo Wellcome FAX/E-mail | Response to FDA Request/Comment | Clinical | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Response to FDA Request/Comment | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 23-Jan-98 | Glaxo Wellcome Correspondence | General Correspondence | Advertising/Promotion | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Request for Comment<br>Press Release | | |
| 27-Jan-98 | Food and Drug Administration Correspondence | Comment/Information Request | Advertising/Promotion | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>Comment/Information Request: Advertising/Promotion | | |
| 04-Feb-98 | Glaxo Wellcome Telephone Conversation | General Teleconference | Other | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Teleconference: Other: Pending Approval of Amerge | | |
| 10-Feb-98 | Food and Drug Administration FAX/E-mail | General Memorandum | Other | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Memorandum: Approval Letter | | |

Application: NDA 20763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg

Date Range: All

| Date | Method of Communication | Document Type | Document SubType | Ser/Sup# |
|---|---|---|---|---|
| 12-Feb-98 | Glaxo Wellcome FAX/E-mail | General Memorandum | Labeling | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Memorandum: Labeling | | |
| 12-Feb-98 | Glaxo Wellcome Telephone Conversation | General Teleconference | Labeling | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Teleconference: Labeling | | |
| 13-Feb-98 | Glaxo Wellcome Telephone Conversation | General Teleconference | Labeling | |
| | | NDA 20-763; Amerge™ (naratriptan hydrochloride) Tablets 1mg & 2.5mg<br>General Teleconference: Labeling | | |

# EXHIBIT 10

Maintenance Fee Receipts for
U.S. 4,997,841

PATENT, DESIGN & TRADE MARK RENEWALS WORLDWIDE
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GLAXO HOLDINGS PLC
ATTN.MRS V.VOLES
GLAXO HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX UB6 0NN

Our ref: 186615/OFRCPT
Your ref:
Date: 19 OCT 1994

Dear Madam

OFFICIAL RECEIPT / RENEWAL CERTIFICATE

| | |
|---|---|
| Country Name: | U.S.A. |
| Type Name: | Patent |
| Patent No.: | 4997841 |
| Reference: | SG329 |
| Proprietor: | GLAXO GROUP LTD |
| Base date: | 05 MAR 1991 |
| Client no.: | 0712117 |
| Annuity: | 1 |

We enclose the official receipt for payment of the annuity indicated above. This document should be kept in a safe place in case proof of renewal is required at any time. If you would like your official receipts stored by CPA in future, please let us know by signing and returning this letter : a fee of £1 for this service will then be added to each future invoice for annuities paid on your account.

Yours faithfully,

Computer Patent Annuities

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
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75L8/0910
COMPUTER PATENT ANNUITIES
C/O COMPUTER PATENT ANNUITITES, INC.
1111 JEFFERSON DAVIS HIGHWAY
SUITE 514, CRYSTAL GATEWAY NORTH
ARLINGTON, VA 22202

DATE MAILED
09/10/94

# MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

| ITM NBR | PATENT NUMBER | FEE CDE | FEE AMOUNT | SUR CHARGE | SERIAL NUMBER | PATENT DATE | FILE DATE | PAY YR | SML ENT | STA |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4,997,841 | 183 | 930 | ---- | 07/231,274 | 03/05/91 | 08/12/88 | 04 | NO | PAI |

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the